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Section of Dermatology

President—H. HALDIN-DAVIS, F.R.C.S.

[*March* 16, 1939]

Kaposi's Idiopathic Multiple Pigment Sarcoma.—LOUIS FORMAN, M.D.

M. Z., male, aged 66. Previously shown January 15, 1931 (*Proceedings*, **24**, 684, Sect. Derm., 38).

Duration of disease twenty-eight years. During the past two months there has been ulceration involving the inner aspect of the left ankle and foot. The ulcer had a definite edge, rolled in parts, and a papilliferous centre. Section of the edge shows epithelial proliferation ; probably a prickle-celled epithelioma.

The progress of the disease during the last eight years has been interesting. The skin of the feet and legs has become sclerotic and smoother, and the brownish purplish infiltrations have disappeared. The skin of the hands is also sclerotic and no longer shows the infiltrations. The areas on the forearms, the most recent to develop, are also partially sclerotic and show spontaneous healing.

Dr. F. PARKES WEBER : With regard to the development of prickle-celled carcinoma in the present case it is interesting to note that the supervention of true spindle-celled sarcoma in a case of Kaposi's so-called multiple idiopathic pigment sarcoma has been recorded by J. H. Sequeira and R. T. Brain in the *Brit. Journ. Dermat. & Syph.*, 1926, **38**, 501.

Lichen Planus Atrophicus.—GODFREY BAMBER, M.D.

Mrs. A. S., aged 50. First seen in October 1938, when the lesions had been present for about two years.

The largest area of eruption covered the lumbosacral region and extended slightly on to the buttocks. Its borders were indefinite. The surface was smooth but uneven, with a variegated appearance due to juxtaposition of small bluish-red and ivory-coloured areas. Patches similar to this were seen over the manubrium sterni and the upper part of the back. A few small patches were scattered over the trunk and limbs intermixed with an occasional typical lichen planus papule. The buccal mucous membrane showed typical lesions. Over the sacrum was a raised warty nodule about 3 × 2 cm.

Histological report (Dr. W. Freudenthal) : (1) A typical lichen planus papule from the left side of the chest : The histology was characteristic of lichen planus.

(2) A red infiltrated lentil-sized nodule surrounded by white atrophic and sclerotic areas in the right scapular region : The epidermis was thin, stretched, and hyperkeratotic. A sharply defined dense lymphocytic infiltrate occupied the upper third of the cutis. Outside the area of infiltration the uppermost part of the cutis was condensed and showed a great number of hyaline blocks staining yellow with van Gieson. Elastic fibres were absent.

(3) A piece of the nodule on the sacrum : This showed extreme hyperkeratosis with down-growing epithelial processes penetrating a dense lymphocytic and plasma-cell infiltration. Outside the warty part the histology was that of lichen planus.

Some of the areas have been treated with Grenz rays; 10 cm. distance, 10 kv. 1,500 r to the right buttock, 1,000 r to the sacral area, 500 r to the manubrium. The areas treated are flatter and more uniform in colour. The warty nodule has been frozen three times, but it recurs.

Dr. H. W. BARBER: This type of atrophic lichen planus is not very uncommon. I have seen two similar cases in the last month. It is not in my opinion the condition described by Darier and Hallopeau under the term "Lichen planus atrophicus vel sclerosus", which is the same as the "lichen albus" of Zumbusch.

Local Diffuse Myxœdema-like Area over Shin.—F. PARKES WEBER, M.D., and H. HUBER, M.D.

The patient (L. P.), is a young married woman aged 24, who had a subtotal thyroidectomy in October 1938 for Graves' disease. Her symptoms improved greatly following this operation. Six weeks ago she suffered from pain in front of the left leg. The pain was not persistent, but there is now a diffuse myxœdema-like thickening in front of the left leg. No X-ray changes can be observed in tibia or fibula.

The appearance of this *diffuse* change differs from the pre-tibial patches of so-called "*circumscribed* myxœdema", which is sometimes associated with Graves' disease, but apparently never with hypothyroidism.

ADDENDUM (March 16, 1939).—The change is practically confined to the left leg. The affected area, about the size of a man's palm, is reddish and bounded above and below by a broad raised ridge, which pits slightly on firm pressure. There is no pain or tenderness. The patient has gained about 6 kilograms since the thyroidectomy, and the basal metabolic rate has gone down from + 76·7% to − 4·5%. The blood-count (March 14) shows nothing abnormal, excepting that there is slight eosinophilia (6%). Brachial blood-pressure 120/80 mm.Hg. Blood-Wassermann reaction negative.

Dr. G. B. DOWLING: I personally thought scleroderma the most likely change. In a small series of cases of scleroderma associated with thyroid disease published by Sequeira some years ago one was a case of myxœdema. After the patient had been under observation for some years she developed two bands of scleroderma, one on each leg.

Reference.—SEQUEIRA, Four Cases of Sclerodermia Associated with Disease of the Thyroid Gland, *Brit. J. Dermat.*, 1916, **28**, 31.

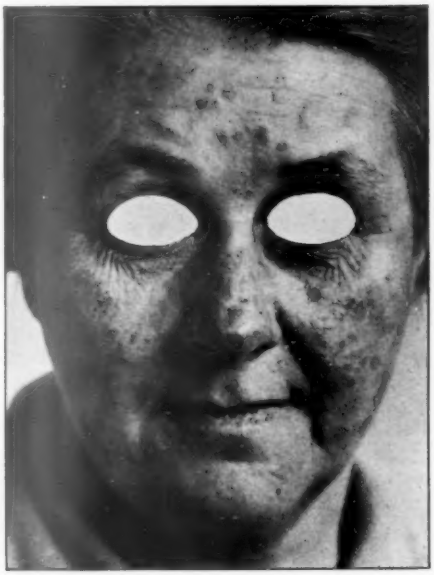
Rosacea-like Type of Cutaneous Sarcoidosis.—F. PARKES WEBER, M.D., and H. K. LAUBER, M.D.

The patient (Mrs. L. H., aged 54), is a rather stout woman (weight 11 st. 9½ lb.) with a blotchy red rosacea-like eruption on her face and forehead. Against the genuine rosaceous nature of the eruption is the fact that similar blotches—some of them obviously raised—are scattered, though much more sparsely, over the trunk and limbs. A small nodule on the right upper arm was excised in August 1936 and microscopically examined. It showed epithelioid "sarcoid" structure with slight giant-cell formation. At that time there was a typical lupus pernio condition on the left side of the nose, but since then the nodules and blotches, though they have greatly increased in number, have undergone some process of involution—at all events they have become paler and more level with the rest of the skin, and only very few are raised and tense as they mostly used to be.

The condition apparently started as lupus pernio on the nose about three years ago, but soon became disseminated. There is nothing else of special significance in the past or family history. Menopause, twelve years ago. The patient has had 11 children, of whom nine are living and healthy, the youngest aged 13.

There is no sign of involvement of the thoracic or abdominal viscera or of the bones or bone-marrow (sternal puncture by Dr. H. Huber). There is no enlargement of the liver, spleen, or superficial lymph-glands. There is no iritis, and the salivary glands are not affected. The Pirquet cuti-reaction is negative. The blood-serum gives negative Wassermann and Meinicke reactions. There has been no fever whilst under observation. Fractional examination of the gastric contents shows nothing abnormal.

Blood-count (February 1939): R.B.C. 5,800,000; Hb. 115%; W.B.C. 6,600 (eosinos. 6%; polymorpho. neutros. 57%; lymphos. 33%; monos. 4%).



Rosacea-like type of cutaneous sarcoidosis.

Urine: Specific gravity 1025; acid; free from albumin, sugar, and excess of urobilinogen; nothing abnormal by microscopic examination.

Brachial blood-pressure: 170/100 mm. Hg. Erythrocyte sedimentation rate is within normal limits.

Radiograms of the thorax and hands (February 1939) show nothing abnormal.

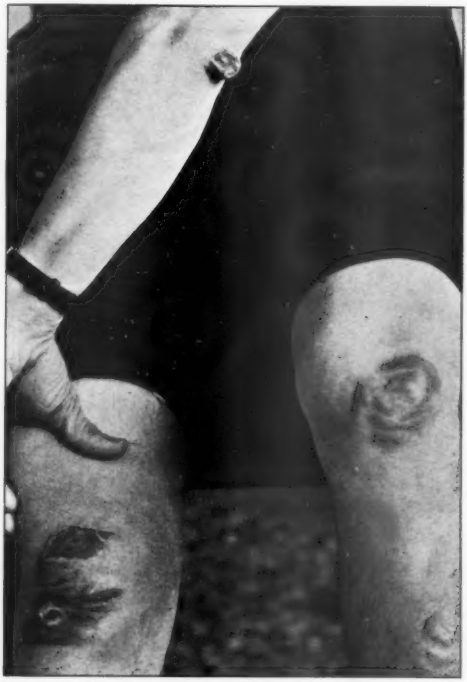
The blood-cholesterol (March 7, 1939) is 280 mgm.%.

Recent treatment by intramuscular injections of sodium morrhuate seems to have made the sarcoid blotches somewhat paler.

Dr. BARBER: I think the prognosis in this case is good. I have had some cases that have done well with Dr. Gray's treatment with sodium morrhuate, and others which have responded to injections of gold.

Ehlers-Danlos Syndrome.—F. PARKES WEBER, M.D., and H. HUBER, M.D.

The patient (P. R.) is a young man, aged 21, who has enjoyed good health. Over both shins he has patches of old atrophic (" papyraceous ") scarring resulting from injuries at football, which he ceased playing two years ago. Over the knees he has infiltrated, somewhat purpuric, areas of scarring, especially on the right side, where there are two ulcers. The skin about both elbows is loose—" cutis laxa " rather than "cutis hyperelastica"—and over the left olecranon there is a cherry-sized loose connective-tissue " pseudo-tumour ". There is a smaller one over the right olecranon.



Ehlers-Danlos syndrome.

The small joints of the hands show over-extensibility. He also shows "so-called" acrocyanosis of the hands without any special tendency to chilblains. There are none of the movable fatty " spherules " in the subcutaneous tissue, which have been a conspicuous feature in some other cases (cf. F. P. Weber and J. K. Aitken, *Proc. Roy. Soc. Med.*, 1937–1938, **31**, 553).

The connective tissue (and fatty) dysplastic pseudo-tumours of the Ehlers-Danlos syndrome are analogous to various vascular dysplastic pseudo-tumours often seen in the Rendu-Osler and some senile dysplastic conditions. It should also be noted that ordinary senile individuals not rarely have a condition of " cutis laxa " (not " cutis hyperelastica ") over the elbows.

Examination of the bleeding time, coagulation time, capillary resistance test, erythrocyte sedimentation, blood-count, and blood-Wassermann reaction shows nothing abnormal in the present case.

The developmental fragility of the skin and its blood-vessels was first noticed when the patient was 7 years old. There is no family history of anything of the kind.

Ehlers-Danlos Syndrome.—W. N. Goldsmith, M.D.

M. E., female, aged 16.

Present condition.—She shows the characteristic flaccid, papery, purplish scars on her knees and elbows and also on her legs. On her right knee is a hemispherical dull purple, soft nodule about 1 cm. in diameter. It can be partially reduced on pressure. Just above and below the knees and elbows the pilosebaceous orifices are prominent. The skin of the face and arms is somewhat looser than normal but it does not amount to a true "cutis laxa". The joints of the limbs are all somewhat over-extensible. This is best seen in the case of the thumbs. No spherules could be felt. In other respects clinical examination revealed nothing abnormal.

Investigations.—Platelet count 220,000 per c.mm. Bleeding time 3 minutes 40 seconds. Clotting time 1 minute 30 seconds. The blood-count was in other respects also normal. Wassermann reaction negative.

Rumpel-Leede test on her arm did not produce an abnormal number of petechiæ, i.e. failed to reveal increased fragility of the blood-vessels.

History.—Her parents cannot remember when the scars on her knees and elbows appeared. She has always bruised easily, and was said to have been born with rickets. She said that she was in hospital some years ago for purpura. In 1927/28 she had abscesses on her knee and arm.

Family history.—Her two brothers and one sister are normal. Of her father's eleven brothers the fifth has had a similar affection. The mother's family are all unaffected.

Ehlers-Danlos Syndrome.—John Lowe, M.D.

When I first saw this girl, who is aged 9, I noticed she had an unusual deformity in the elbow, and clinical examination suggested it might be congenital superior radio-ulnar synostosis. This was confirmed by X-ray examination. On further examination we found three of the four typical features of Ehlers-Danlos syndrome :—

(1) She had marked laxity of the skin especially over the elbows and knees and between the scapulæ.

(2) One point in her history was characteristic. She had fallen down in 1936 and had split the skin right across the patella, exposing the patellar ligament, and was in hospital for three weeks. This long delay in healing is well known, and the surgeon made a note at the time that there was a great amount of effusion. That is also described as characteristic. The typical "cigarette-paper" appearance of the scars on the skin was well shown.

(3) The hyperflexibility of the joints was marked. I think most of you noted the comparative ease with which the patient put her arm behind her back and touched her ear with her fingers, and then she took her heel and touched her umbilicus with it. As regards the fourth feature described in the syndrome—the spherules—for myself I have not been able to find them, but one member thought he could feel a small one over the tibia.

As far as I have been able to ascertain from the literature, this is the first case which has Ehlers-Danlos syndrome combined with congenital radio-ulnar synostosis.

The radio-ulnar synostosis was bilateral and of the first degree. About 50% of cases are bilateral and three degrees are described. First, where there is a union

between the radius and the ulnar at the coronoid fossa ; secondly where there is no head of the radius ; and thirdly where the head of the radius is dislocated either anteriorly or posteriorly.

The girl has a sister about 12 years of age, who is not affected. There appears to be no history of any other member of the family being affected.

Dr. PARKES WEBER : I recently read in a French paper of a case of Ehlers-Danlos syndrome associated with a very striking trigeminal vascular nævus. I have no doubt that such associations of the Ehlers-Danlos syndrome with other developmental dysplasias will be more frequently recorded.

Case for Diagnosis. ? Localized Ichthyosis.—J. E. M. WIGLEY, M.B.

M. P., a girl aged 10, has had the present eruption for about six years. It appears to produce no symptoms, and her general health is unaffected.

Scattered irregularly over the trunk are a number of dry scaly lesions, which look exactly as if hot coins of different sizes had been applied to the skin, and had left these marks. The margin is very sharp, and the affected area appears atrophic.

No fungus could be found, and culture yielded only a " scanty mixed growth of *Staph. albus* and *aureus* ".

Biopsy (Dr. Muende) : " The epidermis is slightly thinned and shows considerable folding. The upper half of the corium is very œdematous and the bundles widely separated, with a peculiar fluffy appearance of the collagen, but there is no increase in the cellular elements. Atrophic skin with no special characteristic signs."

Discussion.—Dr. PARKES WEBER : I think that the abnormal patches of skin in this child are a kind of morphœic atrophodermia, allied to morphœic sclerodermia. An abnormality of the epidermis is present over the patches in this patient. [Dr. Parkes Weber, on later consideration (April 17, 1939) feels convinced that his suggestion at the meeting is wrong and that the case is really one of disseminated porokeratosis Mibelli, i.e. hyperkeratosis centrifuga atrophica, with little horny projections on the atrophic skin of the largest area.]

Dr. GOLDSMITH : I think that it is a localized ichthyosis. The centres of the patches look typically ichthyotic, and the rest of her skin is abnormally dry. But the very sharp demarcation of the patches is quite extraordinary. I feel it is a developmental atrophy, related to ichthyosis.

Dr. I. MUENDE : Histological examination revealed a thinning of the epidermis. On removing the tissue it wrinkled very much, like crêpe paper, and although stretched before it was sectioned, it was still very wrinkled. The only visible change seen microscopically was in the tips of the papillæ where there was a considerable amount of œdema and a peculiar fluffy appearance of the collagen.

? Xantho-Erythroderma Perstans.—J. E. M. WIGLEY, M.B.

C. A. R., an apparently healthy man, aged 44, has had the present eruption for as many years as he can remember. The eruption itches intensely and appears from time to time on different parts of the body. Duration of individual lesions seems to vary, an average being about six months. The distribution is symmetrical on both upper arms, both buttocks, and outer sides of thighs ; to a lesser degree on the legs and chest. The lesions are of a yellowish-pink colour which fade on pressure and are about a quarter of an inch broad. They consist of irregular gyrate figures having a sharply defined edge on the convex side and fading more indefinitely on the concave side. The lesions are scaly and this is made more apparent by gentle scratching. At no time have they been moist or oozing.

Wassermann reaction negative.

Biopsy (Dr. I. Muende): Histological examination revealed slight acanthosis associated with lengthening of the rete pegs. In two small areas there was marked intercellular œdema with intra-epidermal immigration of a few polymorph and

numerous lymphoid cells. Above these areas there was interference with normal keratinization resulting in parakeratosis.

The papillæ were widened and œdematous, and contained dilated capillaries. There was a large number of lymphoid cells arranged chiefly around these vessels.

Although the histological appearances of parapsoriasis are by no means distinctive, the changes in the section under consideration could conform with those of this disease.

Diagnosis.—The clinical appearances of the lesions suggest xantho-erythroderma perstans (Crocker) or parapsoriasis, though the intense irritation is against this.

Discussion.—Dr. MacCormac: I have in the ward a patient whose eruption closely resembles that of Dr. Wigley's patient, except that the condition is more recent and perhaps a little more succulent, and I made a provisional diagnosis of mycosis fungoides.

Dr. Parkes Weber: I have seen some of the earlier cases of xantho-erythroderma perstans shown in England, and so far as I can remember they did not in the least resemble the condition in the present patient, which, in spite of the biopsy, I suggest is one of long-continued *psoriasis figurata*, not of præ-mycotic nature.

Dr. Freudenthal: I have not seen the section, but from Dr. Muende's description I should think it might fit in either with parapsoriasis or with premycosis, which could not be excluded histologically. But psoriasis is unlikely. I gather there is too much infiltration.

Dr. I. Muende: I could find nothing in the section to suggest early mycosis fungoides, for the cellular infiltration did not show the polymorphic types which are characteristic of that disease. As to psoriasis, there was nothing to support this diagnosis histologically even if we were to consider the lesion as being a very old one.

Dr. Wigley: We have examined the case very carefully from the point of view of it being psoriasis. I had the benefit of Dr. Macleod's extremely wide experience, and he came to the conclusion that it was quite definitely not psoriasis. The clinical appearance, though suggestive at a superficial glance, does not fit in if you scratch it and try to get the real silvery scales. The lesions last a short time and disappear and at no time if they are left alone do they show silvery scaling.

Lichen Amyloidosus.—G. B. Dowling, M.D., and W. Freudenthal, M.D.

R. N., aged 58. Café-keeper. Italian.

The eruption appeared first five to six years ago. The onset was rapid and apparently affected both legs and thighs at first, but later cleared up except on the legs, where it has persisted without change. Irritation has been severe since the onset, but especially so during the last six months. The general health is good, and there is no relevant personal or family history.

The eruption encircles both legs from the knee to the ankle, extending on each side up the outer aspect of the thighs; it is more pronounced in front and on the antero-lateral aspect of the legs than on the calves; it consists of acuminate papules densely aggregated and spaced so evenly as to suggest that they are situated about the hair follicles. There are also some scattered papules on the abdomen and on the scrotum. The papules are small and hardly raised in the upper part of the leg, but become progressively larger and more solid from above downwards. They are deeply pigmented.

No clinical diagnosis was made.

Histology (Dr. Freudenthal): In a biopsy from the lower part of the left leg the rete is slightly increased, the horny layer considerably thickened. In the middle of the lesion the horny masses are arranged concentrically forming a central core; here the epidermis is dipping down into the papillary body forming a horny dimple.

The special features of the section are amorphous masses in the papillary body which have replaced the collagen tissue. By higher power these masses are seen to consist of numerous closely aggregated clumps and trabeculæ of varied shape and size ; they stain red metachromatically with methyl violet and grey-yellowish with van Gieson.

The rete pegs overlying the masses are more or less flattened out. There is hardly any inflammatory reaction.

Diagnosis : Lichen amyloidosus.

POSTSCRIPT.—A second biopsy from the upper part of the left leg shows a very similar histological picture with a great amount of amyloid in the papillary body.

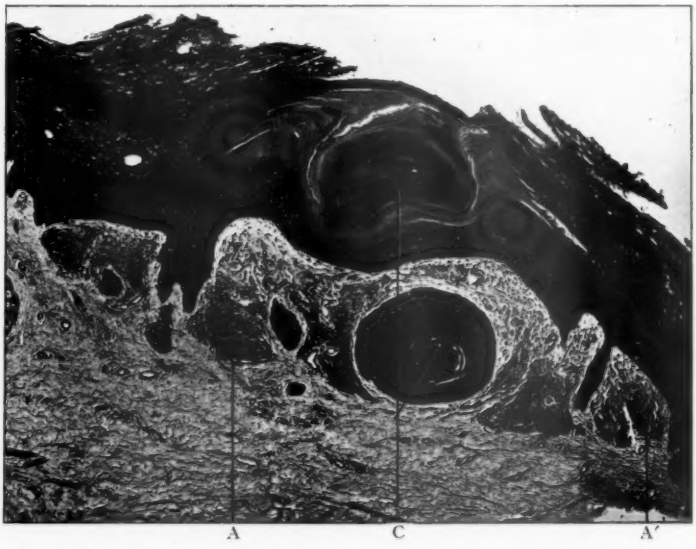


Fig. 1.—× 70. Methyl violet reaction. A, A′, Amyloid masses in the papillary body. C, Central core with horny dimple.

The horny layer, too, contains a number of small clumps of amyloid indicating that it is in the process of being eliminated. (Compare figure facing page 145 in W. A. Goldsmith's " Recent Advances in Dermatology ".)

A third biopsy of normal skin from the right leg shows no amyloid.

Dr. FREUDENTHAL : This is the second case of lichen amyloidosus shown here, the first being shown five years ago by Dr. Gray (*Proceedings*, **1934**, **27**, 1462, Sect. Derm. 74). I think it was then said to be nothing but lichen planus with amyloid degeneration. The section does not support that idea. You will note that there is no infiltrate at all. There is no inflammatory change. There are other reasons which make it unlikely that lichen amyloidosus is a degenerated lichen planus. This section makes it particularly clear that on histological grounds there is no support for the idea that lichen amyloidosus is a lichen planus with secondary deposits of amyloid. Lichen planus is characterized by a very dense lymphocytic infiltration under the epidermis.

Lymphatic Leukæmia with Skin Deposits.—C. M. NORMAN, M.B. (introduced by Dr. FORMAN).

J. B., aged 42.

Three months' history of loss of weight (10 lb.), poor appetite, and pains in arms and legs. Rash appeared over trunk, three months ago. Glands in axillæ and epitrochlear region were noticed to be enlarged a month ago and spleen found enlarged 3 in. below costal margin. Liver also palpable. The rash consisted of small, brownish, slightly raised papules, some of which were hæmorrhagic. This eruption suggested pityriasis lichenoides. There were also purplish raised infiltrated areas, increasing in size and becoming confluent over the back.

Blood-count: R.B.C. 3,900,000; Hb. 80%; W.B.C. 185,000, lymphos. 97%, polys. 3%. Hyalines 1%. Platelets 47,000.

Biopsy of one of the purplish infiltrations and one of the small papules showed dense uniform infiltration with lymphocytes of the cutis and subcutaneous tissue.

Dr. L. FORMAN: When this patient first came up to the out-patients he showed a fairly thick rash consisting of very small brownish macules some perhaps a little infiltrated and some a little hæmorrhagic. It looked like pityriasis lichenoides, but he had one enlarged epitrochlear gland and one small bluish infiltration of the skin on his back which made that diagnosis doubtful. Those small macules were the specific lesions of leukæmia, because the section showed them to be infiltrated with lymphocytes. The purplish infiltrated area over the back cleared up spontaneously after the biopsy.

Lichen Spinulosus and Lichen Planus.—LOUIS FORMAN, M.D.

A. S., aged 38.

Rash appeared four weeks ago. Irritable eruption, thickly distributed on the abdomen and flanks, and to a minor degree over the back and arms. Lesions vary from erect follicles to acuminate follicular papules showing horny spines. Occasional typical lichen planus papules.

Lichen Pilaris Seu Spinulosus.—A. D. K. PETERS, B.M. (for Dr. R. T. BRAIN.)

The patient, a female aged 43, noticed some irritating lesions on her thigh nine months ago. Four months later she had a cervical polypus removed and a diagnostic dilatation and curettage for menorrhagia. A month later an eruption suddenly appeared over the abdomen, which has now become generalized.

When first seen three months ago flat-topped papules were present on the body and there were lesions inside the cheek. The latter have now disappeared and numerous itchy spiny lesions have developed on the body.

The patient now presents four types of lesions:—

(1) Scanty small flat-topped angular papules on the wrist and around the waist.

(2) Atrophic areas the size of a halfpenny, one red and scaly causing a bald area on the scalp, the others pigmented and wrinkled on the left thigh.

(3) Numerous spiny lesions arranged more or less symmetrically as isolated lesions, patches and sheets on the trunk, arms, and thighs, and in a ring on the right arm. Each is greyish yellow in colour and consists of a filiform spine arising from a follicular papule the size of a pin-head. The spine can be picked out leaving a conical depression.

Around the waist these lesions are intermingled with flat papules and some spines can be seen arising from their centres.

(4) Coarse pitting and longitudinal striation of the nails.

Discussion on the two preceding cases.—Dr. MacCormac : I cannot entirely agree with Dr. Forman when he suggests that lichen spinulosus is always lichen planus. There are at least three separate entities which have the structure of lichen spinulosus : a variety met with in children, a tuberculide which, as Adamson has pointed out, is allied to lichen scrofulosorum ; a variety which may precede or be associated with lichen planus, the lichen plano-pilaris of Pringle ; and a third variety accompanied by cicatricial alopecia of the scalp of which a number of cases have been exhibited at the Section.

Dr. GOLDSMITH : I should like to mention another, namely the late stage of a gold, bismuth, or arsenical dermatitis. The eruption often starts rather like acute pityriasis rosea and then becomes more and more lichenoid, and there are nearly always patches of well-developed spiny lesions.

Section of History of Medicine

President—A. P. Cawadias, O.B.E., M.D.

[*November* 2, 1938]

Jundi Shapur—A Sassanian University

By Cyril Elgood, M.A., D.M., F.R.C.P.

In the following pages I seek to trace briefly the history of Jundi Shapur, an ancient city, situated in the modern province of Khuzistan in South-west Persia. To search for its history in the very early ages is waste of energy, for Alexander the Great between 334 and 321 B.C., destroyed all memorials of previous ages which were not inscribed in a non-Persian language or in stone. Yet the town was of an exceedingly ancient foundation. Professor Browne [1] states that it was founded by Shapur I, in the third century after Christ, but I have seen an old Persian manuscript which ascribes to it a much earlier foundation. The writer states that it was built in prehistoric days by the Aryans who named the village Genta Shapirta, which means the Beautiful Garden.

After the death of Alexander the Empire was divided up among his lieutenants. The House of Seleucus, sprung from Iranian and Macedonian stock, ruled the eastern part for a short time until it was displaced by the nomadic tribes of Parthia. No dynasty in historical times has bestowed less upon posterity than did the Parthians, and it was well for Persia that their deadening hand was removed by a young soldier named Ardeshir, son of Papak. This young man, defeating the Parthians in open fight, founded the dynasty of Sassanid, who ruled Persia so successfully until it fell before the Arab invaders. The greatest of the Sassanian monarchs were the two Shapurs. Shapur I came to the throne in A.D. 240. His fame chiefly rests upon his capture of the Roman emperor Valerian. Less dazzling, but of far greater importance, were the later years of his life which he devoted to the arts of peace. His greatest achievement was the building of the dam at Shuster, which still survives. More important for us was his refoundation of the town of Genta Shapirta. As a memorial of his capture of Antioch he renamed the town Veh-az-Andev-i-Shapur or Shapur's Better than Antioch. The old name and the new name were so similar that later generations combined the two to form the name Jundi Shapur, the title by which the town is known to us.

Under royal patronage Jundi Shapur became the chief city of the district. It was peopled, according to Firdausi [2] by Roman and Greek captives. A university was founded and, like Oxford of to-day, it attracted fame as a manufacturing city. Here famous perfumes, the well-known otto of roses, were prepared, and a royal factory for the weaving of carpets was later founded.

Shapur II, or The Great, who had the singular distinction of coming to the throne before he was born and of being crowned *in utero*, patronized the city, enlarged it, and, as some think, was the real founder of the university. That would be about the year A.D. 340.

The town was at the height of its glory when the Arab invasion of Persia occurred. Jundi Shapur surrendered to the Moslem general in 636 and was left undisturbed.

It remained the greatest centre of medical teaching throughout the Islamic world until the growth of the Caliph's capital at Baghdad drained it of its best teachers. Decay then set in. Thanks to its commercial importance the town continued to exist for many years after the University had closed its doors upon its last pupil. A witness in the trial of the wazir Ibn ul-Firat was a man of Jundi Shapur. A little later Ibn Hauqal, a native of Baghdad, writing in the year A.D. 976, says that Jundi Shapur was in his day a fortified city, abounding in all the necessaries of life with extensive date plantations and wheat fields. Ya'qub ibn ul-Lais, the Kharijite general, chose it for his residence on account of its ample resources. Here he died after having conquered all Khorasan and Fars, and when about to attack Baghdad. " He died of a colic. The doctor told him there was no remedy for it but an enema. This he refused to take and preferred dying. His malady, which was a colic accompanied by a hiccup, lasted sixteen days " [3].

The historian Yaqut, who died in 1228, says that he passed the site of the town many times, but that in his day there was no trace of its former grandeur. Yet, as late as 1340, a town still existed there, for al-Qazvini says that it was of medium size and produced much sugar cane [4]. The University had, of course, disappeared long before this. The last official act of the School of Medicine that I have discovered, was the publication of a pharmacopœia by Sabur bin Sahl in 869, which was adopted throughout the Eastern Caliphate and which is probably the first official pharmocopœia ever to be issued. Sooner or later after this the School disappeared, for al-Jurjani, writing about 1125, speaks of prescriptions which " used to be employed in the Hospital at Jundi Shapur " [5]. Nevertheless, the traditions of the School endured. Al-Ansari in his Ikhtiyarat-i-Badi'i repeatedly refers to formulæ which he ascribes to al-Khuzi. In this I see, not the name of a man, but the district of Khuzistan, that is Jundi Shapur [6]. In the various Christian terms applied to many of the elaborate pharmacological preparations of Islamic days, such as the Messianic Electuary and the Bishops' Electuary, I am inclined to believe that we have a survival of the time when Persian medical education was in the hands of Christian teachers.

I was myself in the neighbourhood of Jundi Shapur in 1930, but alas could find no trace of its ancient glory. According to Rawlinson the village now called Shahabad, a few mud walls and some trenches, is all that remains of this well-populated and justly celebrated city [7].

Many questions arise in considering this primitive university. We are specially concerned with considering how the Faculty of Medicine stood with regard to other Faculties. I am inclined to think that it lay third in importance and possibly that means last. Theology and Philosophy would certainly rank senior to Medicine. The University was essentially an ecclesiastical foundation. Medicals as well as divines were compelled to attend a daily service before settling down each to his own study. Furthermore, the town of Jundi Shapur was the seat of the Nestorian Metropolitan, and it is not likely that in those days the priest would yield primacy to the physician. Nevertheless the argument is not a strong one, for in those days of faith Medicine and Religion were closely allied, and many of the clergy of Jundi Shapur were also practising physicians.

So strong was the Christian element in the city that it was at Jundi Shapur that Mani, the arch heretic and founder of the sect of the Manichees, was tried and executed. Firdausi tells of his death :—

> " This worshipper of pictures is unfit
> To live, so, since he causeth turmoil here,
> Flay him from head to foot, and let his skin
> Be stuffed with hay, and then, that no one else
> May make pretence to like dignities,
> Hang up the skin upon the city gate
> Or on the wall outside the Hospital " [8].

The gate where the stuffed body was exposed was known thereafter as the Mani Gate.

The type of Medicine which was inculcated there must have been predominantly Greek. Yet it was not exclusively Greek, for al-Qifti says :—

> " They made rapid progress in Science, developing new methods in the treatment of disease along pharmacological lines so that their therapy was judged superior to that of the Greeks and the Hindus. Furthermore, these physicians adopted the scientific methods of other peoples and modified them by their own discoveries. They elaborated medical laws and recorded the work that they had done " [9].

Indigenous Medicine, Indian Medicine, and possibly Chinese Medicine, must all have been represented in the School.

The Hippocratic System had, of course, a long start over other systems. The Achæmenian kings replaced their Egyptian advisers by Greek practitioners. Alexander the Great employed only Greek doctors for himself and his staff. The Seleucids continued to use Greek as their official language and to model their training and education upon Greek ideals. Even the rude Parthians could not resist Greek culture, and soon became persianized and philhellenes, adopted Iranian names and adored Zoroastrian divine beings.

As though this atmosphere was not enough to guarantee the supremacy of Greek tradition in Jundi Shapur, the University received a succession of teachers who knew no other system except the Hippocratic. First came the Nestorian exodus from Edessa in 489. The Council of Nicea had defined the doctrine of the Trinity. Nestorius, the protagonist against the Catholic view, was excommunicated for heresy, and the people of Edessa preferred to side with him and oppose the Pope. Their university became the headquarters of the new heresy and in due course was excommunicated. To silence it in 489 the emperor Zeno ordered the gates to be closed and teaching to cease. The order was obeyed and the medical students and their professors, deprived of a school, went as a body to Jundi Shapur.

A second exodus, this time of the neo-Platonists from Athens in 529 in order to avoid the harsh edicts of Justinian, forged yet another link between the Greek tradition and Persian teaching.

Besides these mass movements there was a continual trickle of individual Greek doctors from the West to the East. A few are known to us by name. A Greek physician accompanied the daughter of Aurelian on the occasion of her marriage to Shapur I and, according to Bar Hebraeus, was the first to teach publicly in Jundi Shapur the Hippocratic System [10]. Another, named Theodosius, was the favourite of Shapur II, to whom he showed his favour by having a special church built for him [11]. His System of Medicine is mentioned as one of the few Persian books on Medicine which were later translated into Arabic after the Arab invasion.

The emperor Kai Kubad was attended by a Byzantine physician named Stephen of Edessa, who also had the task of schooling the young Anushirvan. That sovereign on coming to the throne, chose as his personal physician a Roman named Tribunus whom he valued so highly that, when he negotiated a five-years' truce with Rome, he stipulated that Tribunus was to return to his service. The custom of employing Greek doctors survived the Islamic times, for we find that al-Hajjaj ibn Yusuf, the Arab conqueror of Persia, had attached to him a Greek physician whom the Arab biographers named Thiyazuq (? Theodokos). His is the first recorded case of a gastric test meal. For when his master was ill with indigestion, he made him swallow a lump of meat at the end of a string. After half an hour he pulled up the string and found the meat riddled with worms. He thereupon declared the case to be one of cancer of the stomach. And in due time al-Hajjaj died of it [12].

The language in which the teaching of the University was carried out is an interesting detail, for until the Islam became supreme in the Middle East there was no *lingua franca*. I feel sure that Syriac must have been the official language of the University. The predominant position of the clericals would assure that. The lectures given in the School of Medicine were probably also in Syriac, though some of

the teachers may have used Persian, Arabic, or Greek. The Byzantine physicians probably used this last language, and there may well have been Greek-speaking students. A medical congress held in the University during the days of Anushirvan is said to have been attended by al-Tasyufatai, which may be an Arabic rendering of the sect of the Sophists [13]. On the other hand, the great family of the Bukht Yishu', which provided the Chief Physician of the School for so many years, were Syriac Christians. Their name is Syriac and to them Syriac must have been the mother tongue. When Bukht Yishu' first went to Baghdad, the Caliph was astonished when he greeted him in Arabic and Persian [14]. Furthermore, Hunayn went to Basra when he wished to make a thorough study of Greek before commencing his translations. All this seems to show that neither Greek nor Arabic nor even Persian were the usual languages of the School. A chance quotation shows that the School used, in fact, a local dialect for scientific purposes, for an Arab physician is quoted as ascribing the smallness of his practice to the fact that he cannot speak the language of Jundi Shapur. And the author of the Manahij-ul-Fikar explains this by adding that they had a jargon of their own [15].

Finally, there has to be considered the question of the importance of Jundi Shapur in the History of Medicine. It is not known that any of its professors made any important contribution to the corpus of medical knowledge. But the part that the University played is the part of a keystone in the bridge which links Hippocrates to Harvey. With the death of Galen Western Medicine began to sink until it was revived through the medium of Arab translations. The store-house of Western Medicine during the years of stagnation was Jundi Shapur. The blood which set beating the heart of Baghdad came from Jundi Shapur. The Bukht Yishu's, Hunayn, (Johannitius), Yuhanna bin Masawayh (Mesue), and a host of less-known men were trained in Jundi Shapur. They came, many of them unwillingly, to Baghdad to found there a Medical School that was unrivalled in its day. Jundi Shapur was bled to death to transfuse life into the infant School of Baghdad. The modern Iran, which likes to look back on the native glories of her country which owe nothing to Arab influence, may well count the University of Jundi Shapur among her greatest triumphs.

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Section of Odontology

President—A. H. Parrott, O.B.E., M.D.S.Birm.

[*March* 27, 1939]

Cases shown by R. S. Taylor, M.R.C.S., L.D.S.

Naso-Palatine Cyst.

Patient, male, aged 34.

Family history.—Nothing relevant.

23.12.37: Seen in ear, nose and throat department complaining of catarrh and pyrexia of three weeks' duration.

29.12.37: Swelling in anterior part of palate. X-rays showed cyst in mid-line. Sent to dental department. It was thought that the cyst might have involved incisor teeth.

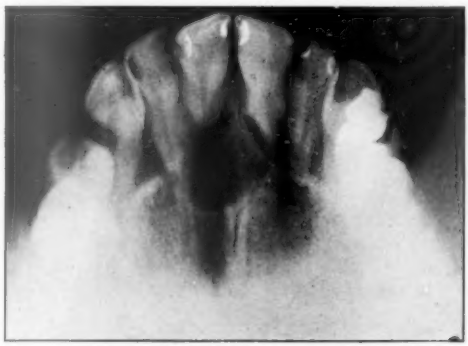

Fig. 1.—Naso-palatine cyst showing appearance in December 1937, before operation.

Operation under intratracheal anæsthesia. Mucoperiosteal flap formed, bony spur chipped away, and cyst opened. The wound was not closed. Recovery uneventful, healing by granulation.

The cyst was not connected with the teeth nor had it involved them. Section of tissue removed showed dense fibrous tissue only.

Large Granuloma of Mandible.

Patient, male, aged 56.

Personal history.—$\overline{7}\ \overline{5}\ \overline{4}|$ teeth removed November 1938. Swelling occurred after this and was associated with loss of sensation in lip and chin on right side. Swelling increased.

First seen by Mr. Taylor 31.1.39. Admitted to Westminster Hospital 23.2.39.

On examination.—Swelling right mandible $3\ \overline{to\ 7}|$ region. Inner and outer plate expanded, swelling not tender. No enlarged lymph-glands.

X-rays showed irregular bone structure, haziness of trabeculation and rarefaction, no periosteal reaction. Suggests cystic change filling in.

Operation under nitrous oxide and oxygen. Contents of swelling curetted out. Frozen section. Report of non-malignant tissue. Suggests chronic inflammatory tissue. $3\ 2|$ removed, cavity swabbed out with pure carbolic acid, and left open to drain.

Diagnosis was between a malignant and inflammatory condition. Inflammatory condition diagnosed by clinical history, examination, and X-ray findings. Confirmed at operation by frozen section and later by decalcified tissue section.

Postscript (30.6.39).—This has now developed into an osteomyelitis of the mandible of the honeycomb type. The infection is still active. Actinomycosis suspected but all tests negative.

Osteoclastoma of Mandible.

Boy, aged 10 years.

Family history.—No information of similar condition in any relation.

Personal history.—Epulis removed $\overline{d\ e}$ region, 1936. Growth removed; radium treatment 432 mgm. hrs., 1938. Sent to Westminster Hospital 20.12.38.

On examination.—Large diffuse swelling $|\overline{3456}$ region, expansion of both inner

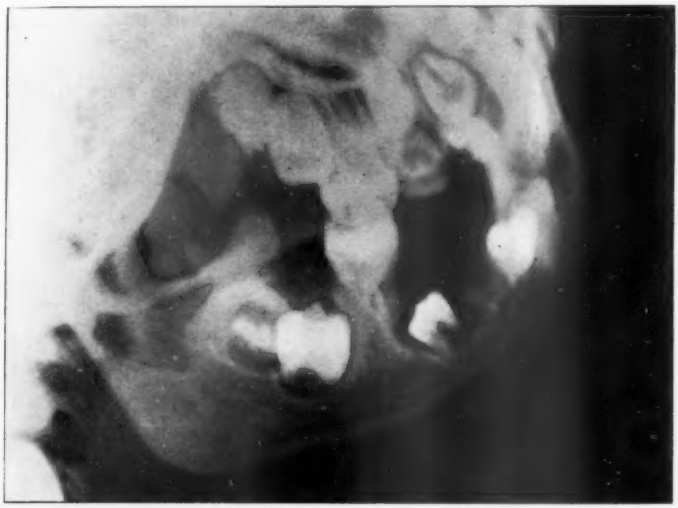

Fig. 2.—Osteoclastoma of mandible, showing X-ray appearance December 20, 1938, before operation.

and outer alveolar plate. Lymph-glands not enlarged. X-rays showed expansion of jaw with very fine trabeculations.

Operation under intratracheal nitrous oxide and oxygen. Incision from incisor region to molar region. Buccal flap raised, care being taken to include periosteum and not part of tumour. |2 extracted, outer plate removed, germs of |345 spooned out of growth, |6 extracted, tumour dissected out, cavity curetted, and sharp edges smoothed off.

Sections show typical osteoclastoma rich in giant cells.

No recurrence as yet, but the patient is being kept under careful observation.

POSTSCRIPT (30.6.39).—Report from patient's own doctor: no signs of recurrence.

Osteitis Fibrosa of Left Upper Jaw Involving Base of Skull. Osteitis Deformans of Spine.—E. R. GARNETT PASSE, F.R.C.S.

Mrs. E. D., aged 55.

Personal history.—Seven years: Onset of pain and swelling of left cheek and under left eye.

On examination (1933).—Smooth, hard, painless swelling limited to the junction of the superior maxilla and malar bones of the left side. Biopsy: Osteitis fibrosa. Swelling increased in size and enlargement spread to alveolus. Pain more pronounced. 1938: Blood calcium investigation proved normal balance.

On examination (1938).—Generalized increase in size of left maxilla, extending into mouth, nose and orbit, and posteriorly into the sphenopalatine fossa, slightly tender. Stereoscopic X-ray photographs revealed that the change extended into the base of the skull in the sphenoid region also.

It was therefore thought that operative procedure was out of the question.

Treatment.—Deep X-ray therapy will be tried in an endeavour to relieve the pain as well as to attack the pathological process.

X-ray reports: 14.2.39—Skull: The thickening at the base of the skull in the middle fossa indicates that the process has spread to this region. This appearance is quite typical of localized osteitis fibrosa, but it is impossible to rule out sarcomatous changes.

23.2.39: Thoracic and lumbar vertebræ: Increased density of practically the whole of the pelvis, bodies of the 4th lumbar and 7–8th dorsal vertebræ. Radiologically it is very difficult to say whether this is Paget's disease or focal osteitis fibrosa, but appearances are rather more suggestive of Paget's disease.

Osteitis Fibrosa of Left Superior Maxilla.—E. R. GARNETT PASSE, F.R.C.S.

Ronald M., aged 14.

History.—Three years ago swelling of left side of hard palate and on the outside of the face. A piece was taken for section.

Pathological report: Osteitis fibrosa of superior maxilla. Replacement of superior maxilla and adjacent tissues by a circumscribed mass of mostly solid dense fibrous tissue containing a few small cysts, numerous areas of osteoclasts, numerous areas of formation of woven bone, and large osteoblasts.

March, 1936: Excision of maxilla by Mr. Norman Patterson, with very good result. The cheek has been built out by means of an obturator, but retraction by scarring was a serious difficulty. This was treated by an epithelial inlay on February 8, 1938, by means of a Thiersch graft. The graft took satisfactorily, but scarring tended to involve the cheek. It is intended to perform a further plastic operation to give better facial symmetry.

[*April* 24, 1939]

The Histology and Histopathology of the Dental Innervation

By Robert Bradlaw, M.R.C.S., L.R.C.P., L.D.S.

Abstract.—The presence of a perivascular neural plexus in the periodontal membrane suggests that the dental structures have both sensory and autonomic nerve supply. The fibres described by Mummery are unaffected by section of the inferior dental nerve although there is marked degeneration in all demonstrable nerves. Nerve-fibres have been observed describing simple and complex looping in the odontogenetic zone and others which, running tangentially between the odontoblast layer and the dentine, form a very definite nerve plexus. Attached to these nerve-fibres are numerous round or pear-shaped bodies which may be either nerve-cells or end-organs. Definite nerve-fibres have been traced into the dentine. The convoluted forms described by growing nerve-fibres approaching transplanted teeth did not resemble the nerve-loops previously reported in the periodontal membrane of monkey and man. Plexiform nerve-fibres have been seen in the gum of the cat and varicose nerve-fibres in the gum of the sheep. In man, intra-epithelial fibres have been observed which pass from the intra-papillary neural coils to terminate near the surface of the epithelium in knob-like endings. No abnormality of innervation has been found in supernumerary teeth and teeth from cleft palates, dentigerous and ovarian cysts, and in the pulps of denticles from compound odontomes. Since there is no difference in the innervation of heterogenous and autogenous tooth-germ transplants, whether of normal or abnormal form, it would seem that abnormalities of form are not due to abnormal innervation. The development and degeneration of the peripheral nerves and the changes produced in the dental innervation by local and general disease in man and experimental animals are described and discussed.

Résumé.—L'existence d'un plexus neural périvasculaire dans la membrane parodontale suggère que les structures dentaires ont une innervation sensitive et autonome. Les fibres décrites par Mummery ne sont pas atteintes par la section du nerf dentaire inférieur, bien que tous les nerfs démontrables soient très considérablement dégénérés. On a observé des fibres nerveuses qui décrivent des boucles simples et complexes dans la zone odontogène, ainsi que d'autres, passant tangentiellement entre la couche odontoblastique et la dentine et formant un plexus nerveux bien défini. De nombreux corps ronds ou en forme de poire, qui représentent soit des cellules nerveuses soit des organes terminaux, sont attachés à ces fibres. Des fibres nerveuses nettes ont été tracées jusque dans la dentine. Les sinuosités formées par les nerfs croissant envers des dents transplantées ne ressemblent pas aux boucles dans la membrane parodontale de l'homme et du singe qui ont été décrites antérieurement. Des fibres nerveuses plexiformes ont été observées dans la gencive du chat, et des fibres variqueuses dans celle du mouton. Chez l'homme on a observé des fibres intra-épithéliales, venant des boucles intra-papillaires et passant presque jusqu'à la surface de l'épithèle, où elles se terminent en forme de bouton. Aucune anomalie de l'innervation n'a été observée dans les dents surnuméraires, ni dans les dents provenant de cas de palais fendu, ni dans les kystes dentifères ou ovariens, ni dans les pulpes des denticules provenant d'odontomes complexes. Puisqu'il n'y a aucune différence entre l'innervation des greffes autogènes et hétérogènes de germes de dents, il ne semble pas que les malformations soient causées par des anomalies de l'innervation. L'auteur décrit et discute le développement et la dégénération des nerfs périphériques, ainsi que leur altération par les maladies locales et généralisées chez l'homme et chez l'animal expérimental.

Zusammenfassung.—Das Vorhandensein eines perivasculären Nervenplexus in der paradentalen Membran weist darauf hin, dass die Zahngebilde sowohl eine sensorische als auch eine autonome Innervation besitzen. Nach Durchschneidung des N. dentalis zeigten die von Mummery beschriebenen Fasern keine Veränderungen, während alle nachweisbaren Nerven stark degeneriert waren. Es sind Nervenfasern beschrieben worden, die einfache und komplizierte Schlingen in der odontogenen Zone bilden, sowie auch andere, die tangential zwischen der Odontoblastenschicht

und dem Dentin verlaufen und einen einwandfrei nachweisbaren Plexus bilden. Mit diesen Fasern stehen zahlreiche runde oder birnenförmige Gebilde in Verbindung, die entweder Nervenzellen oder Endorgane darstellen. Nervenfasern konnten einwandfrei bis in das Dentin verfolgt werden. Die geschlängelten Gebilde, die bei den auf transplantierte Zähne hin wachsenden Nerven beschrieben wurden, gleichen nicht denjenigen Nervenschlingen, die früher in der paradentalen Membran bei Affen und Menschen beschrieben wurden. Plexiforme Nervenfasern sind im Kiefer der Katze, und variköse Nervenfasern im Kiefer des Schafes beobachtet worden. Beim Menschen sind intraepitheliale Fasern beobachtet worden, die von den intrapapillären Nervenschlingen bis in die Nähe der Oberfläche ziehen, wo sie knopfförmig enden. Bei überzähligen Zähnen, Zähnen bei Spaltgaumen oder in zahntragenden und Eierstockzysten und in der Dentikel-Pulpa bei gemischten Odontomen sind keine Anomalien der Innervation gefunden worden. Da kein Unterschied besteht zwischen der Innervation der heterogenen und autogenen Zahnkeim-Transplantate, gleichgültig ob sie normale oder abnorme Formen aufweisen, scheint es, dass Anomalien der Form nicht auf Anomalien der Innervation zurückzuführen sind. Verf. beschreibt und bespricht die Entwicklung und Degeneration der peripheren Nerven, sowie die Veränderungen, die durch lokale und allgemeine Erkrankungen beim Menschen und bei Versuchstieren herbeigeführt werden.

The Normal Histology of the Dental Innervation

THE teeth are such specialized structures that *a priori* deductions regarding their innervation are inadmissible. Since their function in man differs from that in lower animals, it is not surprising that there are many differences in the way in which they are innervated. Morphological conclusions may not be drawn, however, from a study of their present function and theories of innervation can be properly founded on histological and experimental observation alone.

Anatomy.—Although 22 % of the main peripheral branches of the trigeminal nerve are believed to be unmyelinated (Brashear, 1936), little is known of the autonomic innervation of the teeth and jaws. So far as we are aware, no sympathetic fibres join the trigeminal nerve during its intracranial course (Koch, 1916) and some writers doubt whether it contains autonomic fibres (Leist, 1927, Bremer, 1938). Sympathetic cells, however, have been found in the Gasserian ganglion of man (Kiss, 1932), and parasympathetic fibres are said to be present in the lingual nerve (Marda, 1931). Although there appears to be some difference as to the distribution of the unmyelinated fibres (Windle, 1928, Brashear, 1936), it seems probable that all the dental tissues possess both sensory and autonomic nerve supply and that the latter travel partly in the divisions of the trigeminal and partly as a perivascular neural plexus (Woolard, 1928).

The innervation of the pulpal vessels.—It has been long recognized that there is an intimate association between the blood-vessels and nerves of the pulp (Walkhoff, 1897, Fischer, 1909, *et al.*). A perivascular neural plexus has been demonstrated about the larger vessels (Wellings, 1926, van der Sprenkel, 1936, Mummery, 1912), and unmyelinated fibres accompanying the capillaries are said to communicate across the vessels by a series of oblique anastomoses (Wellings, 1926) or sometimes to describe spiral turns about them (Wellings, 1926, Gordon and Jorg, 1933). The manner in which these nerves terminate is controversial, some observers (Gordon and Jorg, 1933) being unable to find organized endings of any kind and others describing varicose endings in close contact with the endothelium (Ochoterena, 1933), end-plates (Montfort, 1923), and endings in Rouget cells (Wellings, 1926).

The fibres of Mummery.—Mummery (1912) described fibres in the odontogenetic zone that had a " wavy " course but which became straightened out should the pulp separate from the dentine. He considered that these fibres were the axon cylinders of nerve-cells placed at the base of the odontoblasts. As the fibres are unaffected by

section of the main nerve (Stewart, 1927, Bradlaw, 1936) or blood-vessel (Stewart, 1928), although marked changes are produced in all demonstrable nerves, it is concluded that Mummery's fibres are not nerve-fibres. Although it might be argued that decortication of vessels does not invariably produce degeneration of perineural fibres distal to the site of operation (Blair and Bingham, 1928), and that there may be autonomic paths other than those sectioned, the differential staining reactions of Mummery's fibres (Stewart, 1927, Chase, 1929) confirm the conclusions drawn from experimental investigation.

The innervation of the dentine.—Myelinated nerve bundles enter the apical foramina and losing their myelin sheaths in the coronal pulp, break up into numerous filaments to form the so-called " plexus " of Raschkow, but whether the unmyelinated nerve-fibres are distributed in a similar manner is not established. From this zone, nerve fibrils pass towards the odontoblasts and the odontogenetic zone, and here the disposition of nervous elements has been the subject of controversy for nearly a hundred years. This is not due to differences of subjective interpretation only, for chance alone determines whether the plane of a section is to be coincident with the distribution of nerve-fibres in the odontogenetic zone and for this reason histological investigation and experimental methods are limited in their application. Demonstrable continuity with an undoubted nerve bundle is essential before the nervous origin of fibrils can be accepted for truncated nerve fragments and sometimes even a reconstruction by serial section, are open to misinterpretation. Many of the histological techniques used are uncertain in their action and stain connective fibres in the same way as nerve filaments, while post-mortem change, fixation, and decalcification may produce artefacts. As we have already seen, it is quite possible that the pulpal nerve-fibres are of sensory, sympathetic, and parasympathetic origin. We have no reason to assume that the autonomic fibres are distributed only to the blood-vessels, and it may well be that there is more than one method by which the pulpal nerves terminate. The presence of nerve-cells in the pulp (Mummery, Montfort, Calderon) has received very little support. Some writers (Salter, Kolliker, Chase, Munch, Riegele, *et al.*), describe nerve-fibres looping at the inner margin of the dentine, while others (Huber, Dependorf, Calderon, Lewinsky and Stewart, Tiegs, Gordon and Jorg, Riegele, Tojoda), have seen them running in the odontogenetic zone parallel with the edge of the dentine. Some (White, Walkhoff, Gysi, Hopewell-Smith, Noyes, Mummery, Papa, Calderon), believe that they form a network about the odontoblasts, and others that they terminate by free arborization (Walkhoff, Brashear), or by varicosities, or end-bulbs (Bodecker, Huber, Walkhoff, Retzius, Fischer, von Ebner, Hoehl, Woolard, Riegele, Papa, Calderon, Tiegs). Many (Bell, Romer, Dependorf, Mummery, Law, Montfort, Munch, Kani, Tojoda, van der Sprenkel) believe that nerve-fibres enter the dentinal tubules, and some (Morgernstern, Dependorf, van der Sprenkel), describe them winding about Tomes' process, giving off branches which run in the calcified matrix (Morgernstern, Dependorf, Fritsch, Munch, Tojoda, Riegele, van der Sprenkel), and ending in terminal bulbs and arborizations (Romer, Morgernstern, Mummery, Kani, Allen, Tojoda).

I have found nerve-fibres describing simple (fig. 1) and complex (fig. 2) loops in the odontogenetic zone, fibres which pass between the odontoblasts and running parallel with the dentine give off numerous fine filaments (fig. 3) and a very definite nerve plexus (fig. 4) situated between the odontoblasts and the dentine which I suggest may be termed the " marginal plexus ". Sometimes these tangential fibres seem to end as fine arborizations, while at other times they loop back between the odontoblasts. Attached to them may be seen (fig. 5) numerous round or pear shaped bodies. The latter are not unlike the bodies seen by Tiegs (1932) and considered by him to be end-organs in relation to Tomes' processes. They also resemble the varicosities found by Gordon and Jorg (1933), and that figured but not described by Tojoda (1934). While there is nothing to suggest dendritic processes, there is a certain similarity to

the cells shown by Maximow and Bloom (1937) in the Gasserian ganglion of the embryonic guinea-pig, so that whether these bodies are to be regarded as end-organs or as nerve-cells, I am not prepared to say.

I have traced undoubted nerve-fibres into the dentine (figs. 1, 4, 5, and 6), but I am not able to make any contribution regarding the course of the nerve-fibres in the dentine except that in several experiments where I have sectioned the inferior dental nerve in animals for varying periods before the termination of the experiment, fibrils very much like those figured as intratubular nerves by various workers (Mummery, Dependorf, Allen) are still intact in the tubules although there has been complete degeneration of the pulpal and periodontal innervation.

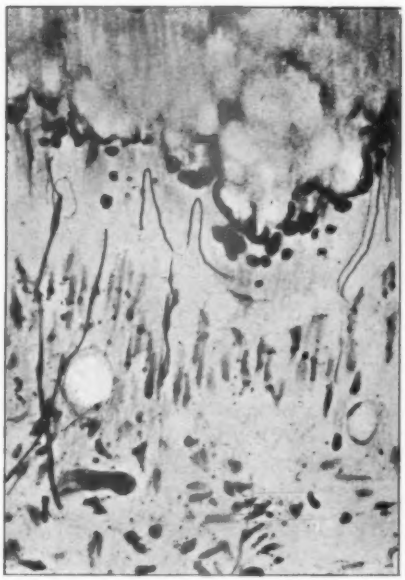

FIG. 1.

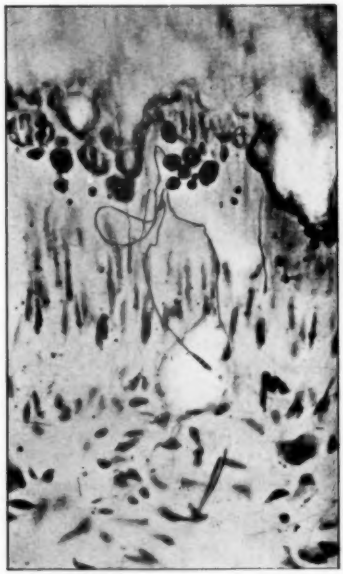

FIG. 2.

FIG. 1.—Simple looping of nerve-fibres in the odontogenetic zone and fibres entering the dentine of an adult human tooth. Stained Cajal. × 300.

FIG. 2.—Complex looping of nerve-fibres in the odontogenetic zone in the pulp of an adult human tooth. Stained Cajal. × 300.

The innervation of the periodontal membrane.—Both myelinated and non-myelinated fibrils are distributed to the periodontal membrane (Windle, 1928). While the main nerve enters from the apical region, accessory nerve bundles enter by perforating the alveolus at different levels (Dependorf, Wedl, Schumacher, Kadanoff, Lewinsky and Stewart). Some of these accessory nerves turn centrally, while others turn towards the gingival margin (Lewinsky and Stewart, 1937). The main bundle traverses the periodontal membrane close to the alveolar bone (Dependorf, van der Sprenkel, Bradlaw, Lewinsky and Stewart) and, passing through the circular ligament, arches over the alveolar crest to be distributed to the gum (Dependorf, 1913, Bradlaw, 1936).

FIG. 3.

FIG. 4.

FIG. 3.—Nerve-fibres ramifying in the odontogenetic zone of the cervical pulp of an adult human tooth. Stained Cajal. × 300.

FIG. 4.—Plexiform nerve-fibres showing minute varicosities in the odontogenetic zone of an adult human tooth. A nerve-fibre is seen entering the dentine. Stained Cajal. × 300.

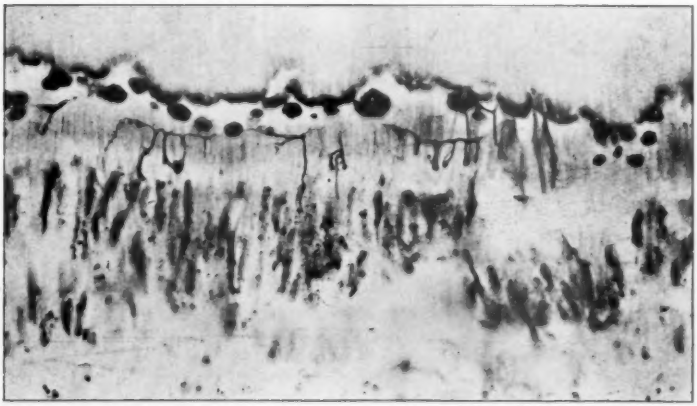

FIG. 5.—Plexiform nerve-fibres in the odontogenetic zone of an adult human tooth. Rounded bodies connected with these nerve-fibres and nerve-fibres entering the dentine are seen. Stained Cajal. × 300.

Anastomoses occur between the nerve-fibres of the periodontal membranes of adjacent teeth (Bradlaw, 1936) and between the nerves of the periodontal membrane, bone, and gum (Dependorf, 1913). It has been found that the periodontal innervation consists of coarse and fine fibres (Dependorf, Windle, Lewinsky and Stewart). The coarse fibres run in the outer part of the membrane and terminate in end-organs which vary in the different types of mammalia (Lewinsky and Stewart, 1937–9), while the fine fibres turn inwards towards the cementum ending in fine ramifications. In the cat the coarse fibres end in the outer part of the periodontal membrane in endings resembling the end-organs of Ruffini or in spindle-like end-organs formed by the nerve becoming twisted like a spiral spring with rounded thickenings on the

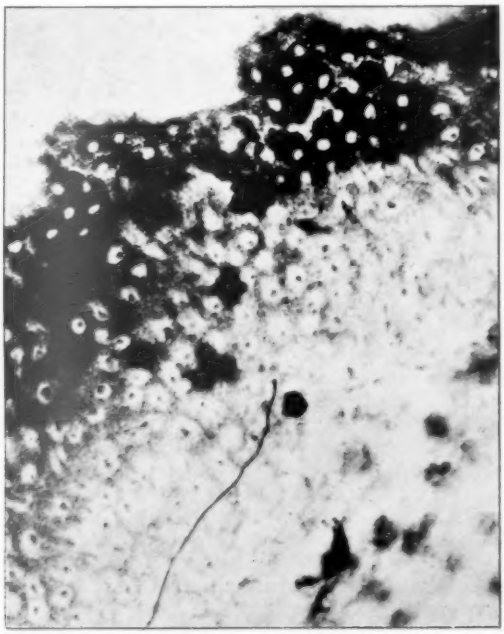

FIG. 6.—Nerve-fibre entering dentinal tubule which is seen in cross section. Stained Cajal. × 750.

convolutions (Lewinsky and Stewart, 1937). In the dog the termination of the thicker fibres closely resembles those of the cat, although their disposition is somewhat different (Lewinsky and Stewart, 1939). In the ferret the arrangement is similar but the end-organs are smaller and less complicated (Lewinsky and Stewart, 1937). The distribution is the same in the rabbit except that the end-organs, which show much variation, are of a coarse branching form with irregular swellings (Lewinsky and Stewart, 1937). In the mole and hedgehog no encapsulated end-organs have been found, but knob-like swellings and fine arborizations are present (Lewinsky and Stewart, 1937). In the mouse, in one investigation (Lewinsky and Stewart, 1937), much the same type of innervation has been reported as that described in other

mammalia together with loop-like forms similar to those found in man (Kadanoff, 1929, Bradlaw, 1936, Lewinsky and Stewart, 1937), and in the monkey (Bradlaw, 1936). Another observer (van der Sprenkel, 1936), however, found periterminal networks lying on collagenous bundles, terminal networks around connective tissue nuclei, and a nervous network from which fibres pass to the dentine to end in very delicate rings inside the dentinal tubules. In the crocodile there are said to be tactile bulbs with connective sheaths of the Krause end-bulb type (Kolmer, 1925). In man the findings show some divergence. In addition to the loop forms in the inner part of the membrane, mentioned previously (Kadanoff, Bradlaw, Lewinsky and Stewart), one investigator (Black, 1887) found some encapsulated endings of the Paccini corpuscle type near the gingival margin, while others describe free terminations and fine arborizations (Dependorf, Black, Ochoterina, Stewart and Lewinsky), club forms (Dependorf), knob-like swellings (Dependorf, Black, Ochoterina, Lewinsky and Stewart), and terminal plexuses (Kadanoff).

As the growing neurofibrils in the tadpole's tail appear to form marked nerve loops, I have transplanted teeth in the path of severed sensory nerves to see if the fibrils growing to the cementum would present coiled or looping forms similar to those seen in monkey and man. Although several convoluted forms were found, they did not in the least resemble the endings to which reference has been made.

The innervation of the gum.—The main nerve supply of the gum has an extra-osseous course, comparatively few nerve-fibres entering from the periodontal membrane (Lewinsky and Stewart, 1938). Although the literature on the innervation of the gum is scanty compared with that on the innervation of the dentine, a bewildering array of terminal apparatus is alleged to be present. Thus, in the frog (Bethe, 1895) the intra-epithelial nerves end either as free arborizations, tripartite endings, or round discs. In the dog, pig, sheep (Merkel, Swerin), and cow (Merkel, Swerin, Jurjewa), tactile discs are said to be present. In the rabbit there is a "tree-like" nerve apparatus (Jurjewa, 1913); in the cat, Vater-Paccini corpuscles, tactile discs, varicose intra-epithelial fibres with button-like endings and leaf-like end-organs Jurjewa, 1913), and in the horse there are unencapsulated coils in the submucosa, varicose intra-epithelial neurofibrils terminating in arborizations, and encapsulated endings (Jurjewa, 1913). In man not only are there loose and close intrapapillary nerve coils (Jurjewa, Kadanoff, Kokubun, Hosaka, Lewinsky and Stewart) from which fibres pass into the epithelium to end in dichotomous division and arborizations (Hosaka, Jurjewa, Kadanoff) or in varicose terminations (Kadanoff, Hosaka, Kokubun, Lewinsky and Stewart), but in the subepithelial layers there are tactile corpuscles (Jurjewa, Kadanoff, Hosaka) Krause end-bulbs (Jurjewa, Kadanoff, Kokubun), cylindrical end-bulbs (Jurjewa, Kokubun, Hosaka), and sickle-shaped intra-epithelial nerve-endings (Kadanoff).

I have found plexiform nerve-fibres resembling the loose subepithelial coils described by Jurjewa (1913) in the cat, and varicose intra-epithelial nerve-fibres running as single fibres to their termination or branching dichotomously in the sheep (fig. 7). I have been able to confirm the presence in man of the loose and close intrapapillary nerve coils found by Kadanoff, Kokubun, Hosaka, and Lewinsky and Stewart (figs. 8 and 9), of intra-epithelial fibres running along the side of the papilla, and of fibres passing from the intrapapillary coils to terminate in knob-like endings (fig. 10) as described by Lewinsky and Stewart.

The innervation of ectopic and abnormal teeth.—For a long time there has been controversy as to whether the pulps of teeth formed in ovarian dermoid cysts (Liebert, Hoelscher, Harris, Wilms, Salter, White and Bland-Sutton, Klemm), and of other ectopic and abnormal teeth were normally innervated.

I have examined the pulps of supernumerary teeth, misplaced teeth from patients with cleft palates, teeth from dentigerous and ovarian cysts, and denticles from compound odontomes, and have found no abnormality of innervation whatsoever.

Autogenous and heterogenous transplant of tooth-germs and parts of tooth-germs (Legros and Magitot, 1874, Huggins, McCarroll and Dahlberg, 1934, Kostecka, 1937) have shown that growth and development may take place far from the jaw. This has been confirmed by the culture of tooth-germs *in vitro* (Glasstone, 1936–38). It has been found, however, that growth often ceased after a certain point had been reached, and the suggestion was made (Glasstone, 1936) that this might be due to the absence of normal innervation.

FIG. 7.—Branching intra-epithelial nerve-fibres with well-marked varicosities in gingival gum of sheep. Stained Cajal. × 450.

I have transplanted tooth-germs, both heterogenously and autogenously, into the crural region of kittens of various ages, but have found no difference in the innervation of the tooth-germs that survived, whether they were normal or abnormal in form. It may therefore be concluded that the abnormalities of development found in transplants (Kostecka, 1938) are not related to their innervation.

The Histopathology of the Dental Innervation

Comparatively little research has been devoted to the histopathology of the dental innervation. If we can recognize degeneration in the nerves supplying the teeth and jaws, it may well be that we will be able to contribute much to the knowledge

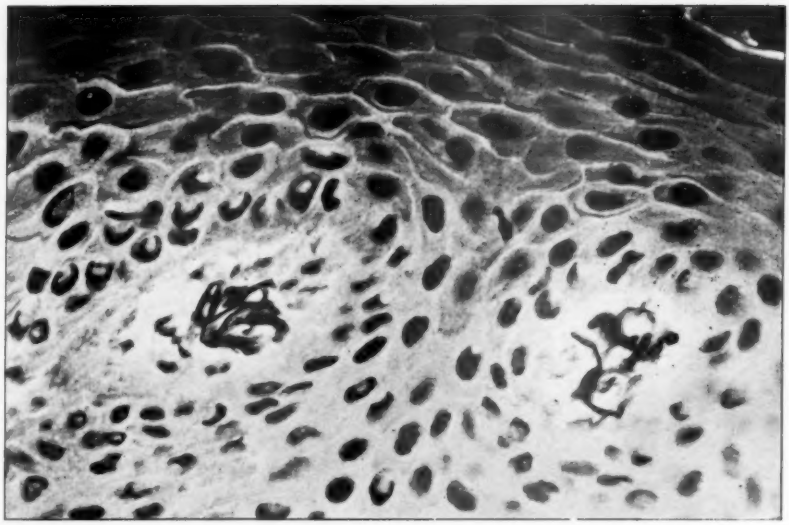

FIG. 8.—Cross section of intrapapillary neural coils in human gum. Stained Cajal. × 450.

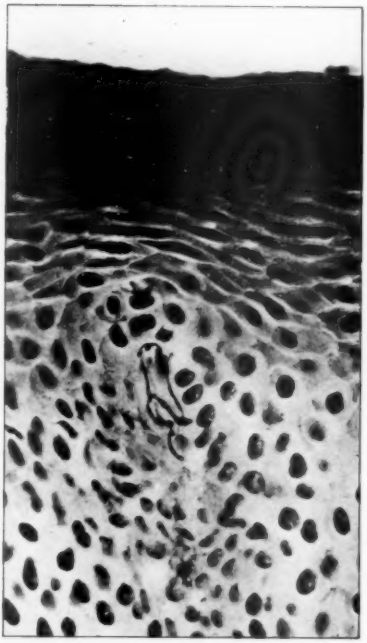

FIG. 9.

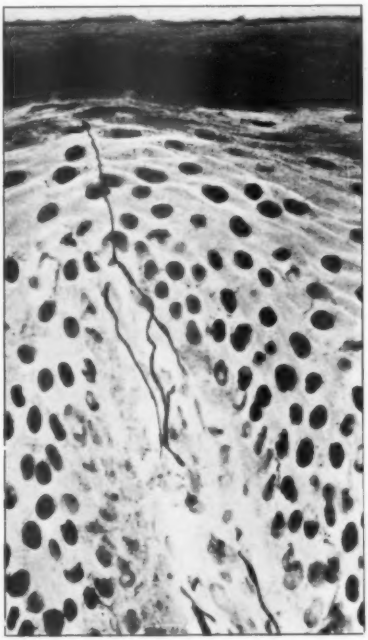

FIG. 10.

FIG. 9.—Interpapillary neural coil in human gum. Stained Cajal. × 300.

FIG. 10.—Intrapapillary nerves in the human gum, from which a nerve-fibre passes into the epithelium to end in a terminal varicosity near the surface. Stained Cajal. × 300.

of local and systemic disease. Unfortunately there is no agreement as to what is fact and what is artefact, while the remarkable similarity between developmental and degenerative processes in nerves has been long recognized (Westphal, Semerling, Oppenheim, Sokolansky).

Development of myelinated nerves.—In a recently published work on the development of myelinated nerves (Sokolansky, 1931), it was stated that an early stage of myelinization is the formation of varicose bundles like " pearl chains ". Later the varicosities become longer and broader and are eventually transformed to the adult

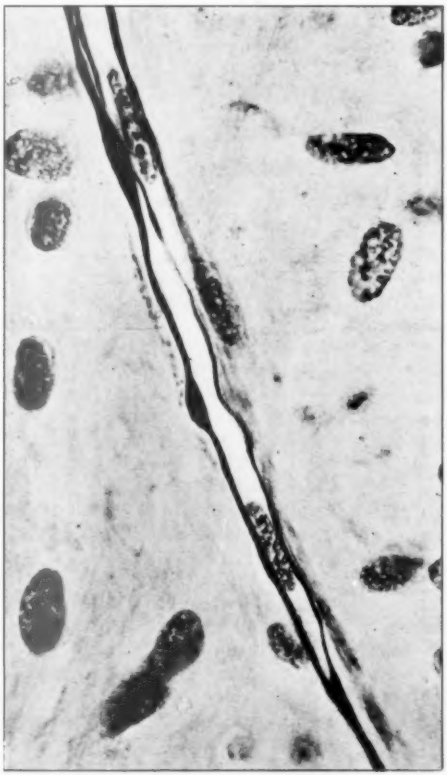

FIG. 11.—Spindle-form enlargements of nerve-fibres of periodontal membrane of fœtal cat. Stained Cajal. × 750.

cylindrical form. Another observer (Speidel, 1935), however, regards these varicosities as an early evidence of irritation.

Degeneration of the peripheral innervation.—In order to decide the category into which abnormal appearances in the dental innervation should be placed, we may compare them with the appearances found in known degenerations produced either by the experimental method or by local and general disease. If a myelinated nerve is sectioned, the peripheral axon first shows some irregularity of contour and then

some local thickening. After some days the myelin sheath becomes granular and the axon varicose or bead-like. Fusiform thickenings are then seen, followed by the formation of globular masses which become successively smaller by slow dissolution. During this time the myelin breaks up into ellipsoids which are phagocytosed. Eventually, a series of proliferated neurolemnal elements and some axonic spherules which have resisted destruction are all that are left (Cajal, 1928). Somewhat similar changes occur as a result of disease. They have been reported in avitaminosis (Eijkman, Hart, Kingery and Kingery, E. Mellanby, Hughes, Duncan, Seifried, Zimmerman, Sutton and Setterfield, *et al.*), in inanition, when the sympathetic fibres are said to be unaffected (Woolard, 1927), in poliomyelitis, where there is vacuolation, myelin destruction, swelling of nodes and the neurokeratin stands out prominently around the axon (Toomey and Weaver), in lead neuritis, where there is vacuolation (Doinikow, 1913), and in other conditions.

Abnormal appearances recorded in the dental innervation.—Many observers (Dependorf, Huber, Hopewell-Smith, Munch, Montfort, Riegele, *et al.*) have recorded varicosities occurring on the course of the pulpal nerves. In some papers they have been figured but not mentioned in the text, while in others they have been noted without comment. One author (Sealey, 1932) described nerve-fibres in the pulp splitting repeatedly to embrace oval structures at regular intervals, while another (Riegele, 1933) found expansions in the course of the pulpal nerves which he regarded as a normal histological appearance. Spindle-shaped or round swellings of different sizes which resembled a string of pearls and were sometimes vacuolated have also been described in the nerves of the dentine (Tojoda, 1934). It was suggested that these were due to post-mortem change, although the nature of other varicosities like short or long cucumbers which did not stain well and which gradually formed small granules and were lost, was undecided.

Degeneration of the dental innervation.—If the inferior dental nerve is cut, the changes that occur are similar to those found after nerve section elsewhere (Stewart, 1927–28, Bucy, 1928). After about two weeks, the myelin sheath is lost and the fibres become markedly irregular and filled with darkly staining ovoids (Bucy, 1928). One observer (Bremer, 1938) showed very definite vesicle formation in the pulpal nerves six days after section. Degenerative changes also occur in the inferior dental nerve if the accompanying artery is ligatured (Euler, 1922, Stewart, 1928). In acute or suppurative pulpitis the myelin of the nerve sheath is the first to be affected, the nuclei of the neurolemma at first staining well (Euler and Meyer, 1927). Following this, the axis cylinders swell and stain irregularly, later fragmenting into bizarre shapes and granular masses (Sigmund and Weber, 1926). Similar degeneration, with vacuolation, has been described in chronic pulpitis (Euler and Meyer, 1927), while marked changes in both axon and neurolemma, and the breaking up of the myelin sheath into fatty droplets are found in the pulpal nerves where arsenic has been applied (Witzel, 1898, Romer, 1909, Wassmuth, 1929) and in experimental animals given a diet deficient in vitamin A (M. Mellanby and King, 1934). In another investigation (Gordon and Jorg, 1933), two types of degenerative change—the " fuseau de retraction " and " spherule hypoargentophile " were found in the nerves of the pulp. As these appearances were seen in preparations where the pulp and the nuclei of the pulpal cells stained normally, they were thought to be degenerative changes, similar to those seen in certain diseases of the central nervous system and not artefacts.

I have not infrequently seen spindle-like enlargements of the nerve-fibres of the periodontal membrane (fig. 11) and pulps of fœtal and very young cats. Perhaps these are stages in the development of the nerves. In fracture of the mandible I have found marked fragmentation and sometimes vacuolation in the pulpal nerves of teeth anterior to the line of fracture (fig. 12). Thickening and varicose changes have been observed in the pulpal and periodontal innervation in pyorrhœa (figs.

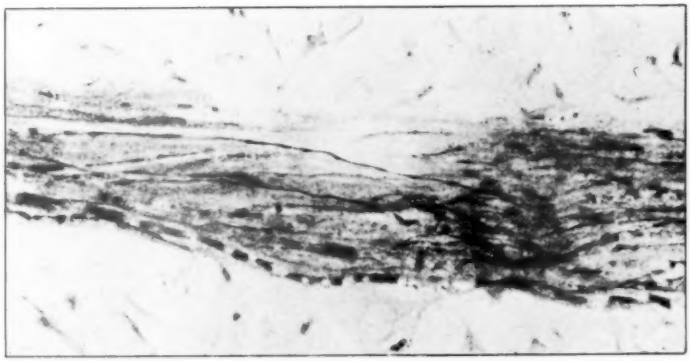

FIG. 12.—Fragmentation and vacuolation of nerve bundle in pulp of tooth anterior to a fracture of the mandible sustained sixty-eight hours previously. Stained Cajal. × 300.

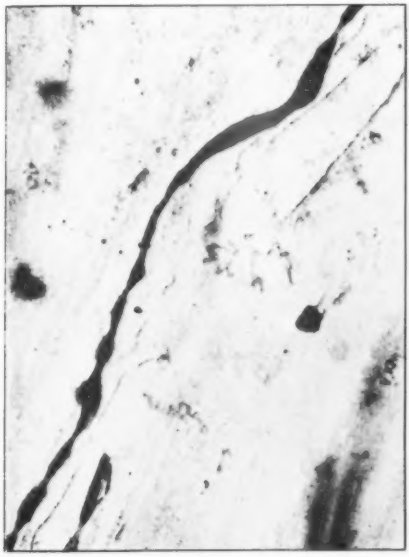

FIG. 13.

FIG. 14.

FIG. 13.—Irregular thickening of nerve-fibres of pulp in a case of pyorrhœa. Stained Cajal. × 750.

FIG. 14.—Abnormal appearance of nerve-fibres in the periodontal membrane in a case of pyorrhœa. Stained Cajal. × 750.

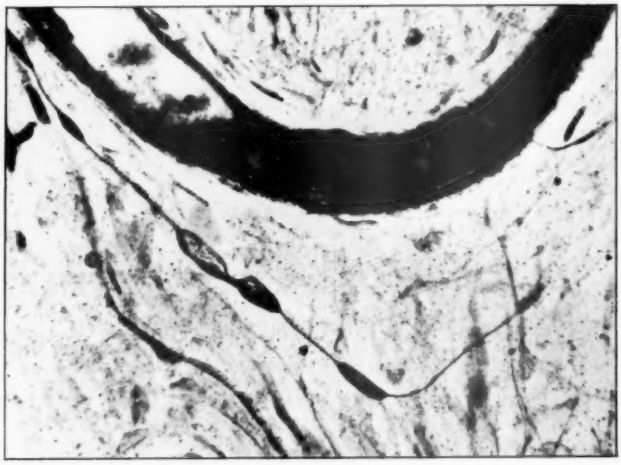

FIG. 15.—Vacuolation of pulpal nerve-fibres in a case of avitaminosis. Stained Cajal. × 300.

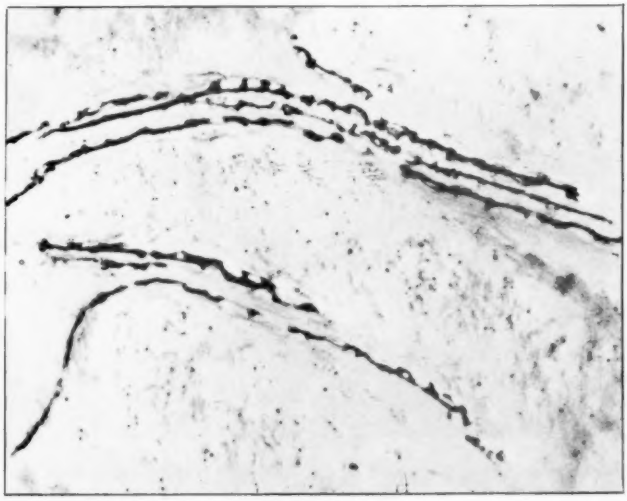

FIG. 16.—Abnormal appearance of pulpal nerves in a case of avitaminosis. Stained Cajal. × 300.

13 and 14), while other appearances resembling the degenerative changes shown by King, Lewinsky and Stewart (1938) in rats given a diet deficient in vitamin A and carotene have been seen in the nerves of the human pulp in avitaminosis (figs. 15 and 16). Fragmentation and varicosities have occurred in the apical and alveolar nerves as a result of extraction and the introduction of toxic material into the pulps of experimental animals has resulted first in a deeper staining with irregularity of

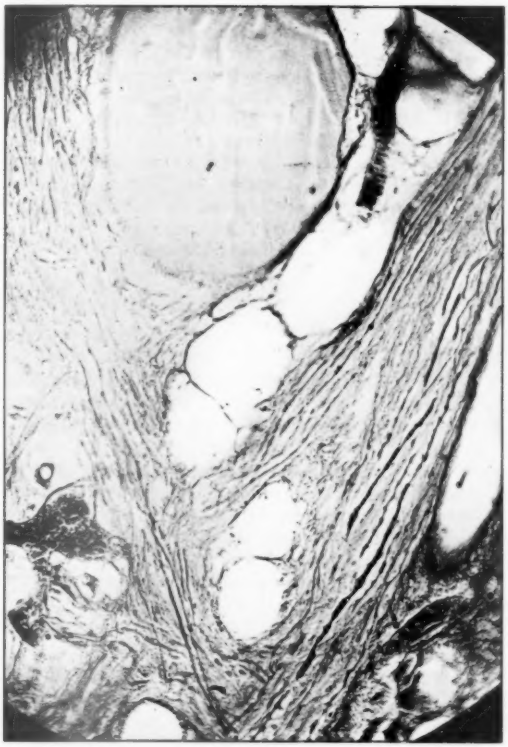

FIG. 17.—Irregular thickening and fragmentation of alveolar nerve bundles in monkey. Multiple extractions had been carried out and toxic material introduced into the sockets seven days before. Stained Cajal. × 75.

contour and then fragmentation with loss of myelin sheath, while similar degenerative changes (fig. 17) with occasional vacuolation of alveolar nerves has followed the introduction of toxic material into extraction sockets.

ACKNOWLEDGMENTS

I wish to thank the Medical Research Council for having defrayed the cost of this investigation, Dr. Stewart and Mr. Gooding for advice on staining methods, Dr. Greenfield for having kindly examined my preparations, and Professor Bernard Shaw and Dr. Ungley of the Royal Victoria Infirmary for much valuable clinical material.

A Comparative Study of the Innervation of the Gum

By D. Stewart, D.Sc., L.R.C.P., M.R.C.S., and W. Lewinsky, M.D.

Abstract.—In this paper we give a comparative study of the innervation of the connective tissues of the gum underlying the epithelium. Our material was taken from carnivores, rodents, insectivores and men. The fibres form superficial and deep plexuses and leashes, and specialized nerve-endings are also present. The types of specialized nerve-endings seen have been :—

(1) Coils which are situated either in the intra-papillary zone of the deeper connective tissue.

(2) Ruffini-like nerve-endings and convoluted fibres the presence of which in the gum has not been previously described.

Résumé.—Les auteurs font une étude comparative de l'innervation des tissue connectifs situés au-dessous de l'épithèle des gencives. Leur matériel est tiré des carnivores, de rongeurs, des insectivores et de l'homme. Les fibres forment des plexus et des boucles superficiels et profonds, et il existe aussi des terminaisons spécialisées. Les types suivants de terminaisons spécialisées ont été observés :—

(1) Des rouleaux situés soit dans la zone intrapapillaire, soit dans le tissu connectif plus profond.

(2) Des terminaisons nerveuses ressemblant à cells de Ruffini, dont la présence dans les gencives n'a pas été décrite jusqu'ici.

Zusammenfassung.—In dieser Arbeit berichten Verf. über eine vergleichende Untersuchung über die Innervation des subepithelialen Bindegewebes des Zahnfleisches. Das Material stammte von Fleischfressern, Nagetieren, Insektenfressern und Menschen. Die Fasern bilden oberflächliche und tiefe Plexen und Schlingen. Es finden sich auch specifische Nervenendigungen.

Die folgenden Arten von specifischen Nervenendigungen wurden beobachtet :—

(1) Schlingen, die entweder in der intrapapillären Zone oder im tieferen Bindegewebe liegen.

(2) Ruffini-artige Nervenendigungen und geschlängelte Fasern, diren Vorkommen im Zahnfleisch vorher noch nicht beschrieben worden war.

In spite of the very large number of papers on peripheral nerve-endings, the number of publications concerning the study of these structures in the gum is relatively small. We have dealt with papers concerning the innervation of the human gum in a previous publication mentioning the work of Kadanoff (1928), Kokubun (1929), Mowry (1930), and Hosaka (1936). The only paper that we found in which comparative anatomical observations on the innervation of the gum were described was published by Jurjewa (1913). Unfortunately, we have to voice the same criticism which we have expressed on previous occasions that although this paper contains a number of elaborate drawings, there are no photomicrographs, which makes it very difficult to compare her results with our own. She describes only the different types of nerve-end structures found in the gum as a whole, and divided the nerve-endings into encapsulated and non-encapsulated. Her drawings are based on her findings in the cat, rabbit, horse, cow, and man, and permit certain conclusions to be drawn. From her descriptions, however, it cannot be determined in which animals the different types of nerve-endings occur, a fact which has already been criticized by Kadanoff.

Our material was obtained from carnivores—cat and ferret ; rodents—mouse and rabbit ; insectivores—mole ; and primate—human. The specimens were prepared by the modification of the Cajal method devised by Gooding and Stewart (1937), and the material used was perfectly fresh, a point of considerable importance in obtaining successful results. Some of the specimens consisted only of gum, while in others the whole jaw and teeth were present as well. The specimens were cut in serial

sections, mainly at 12μ thickness, but in some of the human examples thick sections of 30μ were made.

It is our intention in this paper to confine our observations to the innervation of the connective tissue of the gum, and we shall make only a few incidental references to the innervation of the epithelium.

The actual source of the nerves of the gum is still in doubt. There is no question that a great number of the nerve-fibres have no connexion with the periodontal membrane at all; their course lies just superficial to the periosteum of either the lingual-palatal or buccal alveolar plates. The question of the nerve supply for the gum by periodontal nerves is one of great interest which has not yet been completely investigated. From our observations there seems to be no doubt that the gum does obtain a supply from this source, but it is probably not a rich one. The nerve-fibres for the gum run peripherally in the deeper layer of the connective tissue and are arranged in bundles which divide into smaller ones and approach the most superficial parts of the connective tissue and the epithelium itself. Sometimes these bundles form a definite deep plexus, and a superficial one situated near the epithelium is also present.

This plexiform arrangement of the nerve-fibres corresponds closely to that described in the skin by Woollard (1937). It will probably be wise to define what is meant by plexus, as there has been a tendency to use this term somewhat loosely. The ordinary anatomical conception of a plexus is a structure in which a mesh is formed by fibres passing from one bundle to another without any fusion of individual fibres. This is seen characteristically in a large plexus such as the brachial plexus, and a similar condition is commonly seen microscopically. On the other hand, in recent years certain schools of neurologists have described definite networks in which axon cylinders fuse together, and these are also frequently called plexuses. A certain amount of confusion has been caused by this looseness in terminology. We propose to call those structures in which fusion of fibres occur "anastomoses", and we shall use the term "plexus" when nerve-fibres pass from one bundle to another forming a meshwork. A deep plexus has been seen in the gums of all the animals which have been studied. It has always the same general form and is well illustrated in the deep plexus of the rabbit in fig. 1. The main bundle lies in the deeper part of the tissue from which smaller fibres arise to form the plexus. From the plexus, secondary bundles pass out towards the periphery.

On a more superficial plane a second plexus is frequently formed which lies near the epithelium. It may be formed by fibres arising from the deep plexus or directly from nerve bundles coming from the deeper layer without the intervention of a deep plexus. In these deeper structures which we have just described, we have no doubt that we are dealing with a true plexus, and there seems to be no fusion of individual fibres. In the superficial structures, however, it is not possible to make such a definite statement, and this may be one of the causes of confusion in terminology to which we have already referred. We are under the impression that along with the plexiform arrangements there is also sometimes present a true anastomosis of fibres, and this agrees closely with the views enunciated by Woollard. Like him, we do not deny the validity of the neurone theory, because these fibrillar anastomoses may be due to the splitting and re-fusing of collaterals of single axon cylinders. An example of a superficial plexus formed from a deep plexus in the human is seen in fig. 2. In this specimen there appears to be a true anastomosis of fibrillæ. We have not been able to satisfy ourselves that anastomosis is always present in the superficial network and in some cases it forms a superficial plexus as shown in fig. 3, from the gum of the cat. In the mole, however, we have seen amongst other structures another arrangement of nerve-fibres in the connective tissue. Here the nerve bundles often form themselves into leashes.

Woollard put forward the hypothesis that these anastomoses can be considered

to be diffuse end-organs for pain. Besides these diffuse end-organs, however, there are also present others of a more definite structure. These can be divided into two groups :—

(1) A subpapillary group.
(2) An intrapapillary group.

The end-organs in the subpapillary group seem to be formed by one or several thick fibres which are often accompanied by thin ones, an arrangement which is frequently found in other parts of the body. In fig. 4 an example of one of the subpapillary nerve-endings which were found in the ferret is illustrated. It consists of a thick convoluted fibre, which closely resembles the type 1 nerve-ending which we have already described in the periodontal membrane of that animal. Subpapillary endings have also been seen in the subpapillary tissues of the cat which have a structure similar to that of the type 1 endings in the periodontal membrane of that animal.

Fig. 5 shows a human gum containing a complex convoluted structure formed largely by thick nerve-fibres, but thin ones are also present. Having formed these

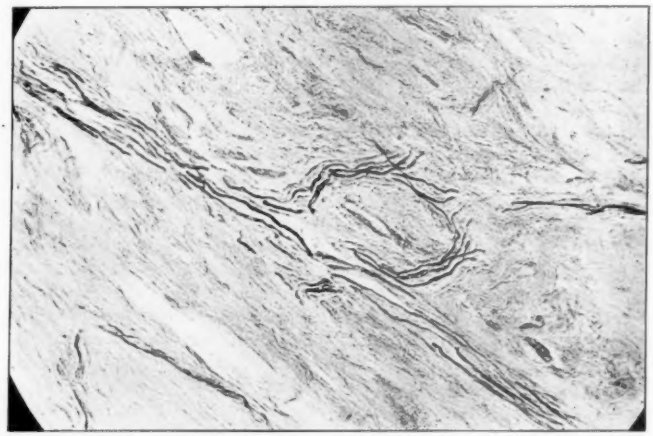

FIG. 1.—Deep plexus (Rabbit).

convolutions the nerve-fibres continue their course. This organ clearly differs in structure from those which we have described above in the carnivores, and it does not correspond to anything which we have been able to find in the periodontal membrane in man. It is also placed in a deeper plane in the connective tissues. In the mouse we have found curious convoluted nerve-fibres lying deeply in the connective tissue as seen in fig. 6. They are found only in that part of the gum which lies in close relationship to the underlying muscles, and have not been seen in other parts of the gum. The fibres correspond in appearance to the nerve-fibres in the muscle and are in continuity with them. It is therefore possible that functionally they are muscle sense organs.

In the subpapillary region we were only able to find coils in certain animals. In an earlier paper (1938*a*) we have described such an end-organ in the rat and we have now found a deep coil in this region in the cat (fig. 7). In this animal, however, this structure is encapsulated and the fibres are thicker than those in the rat. These deep coils, however, appear to be rather sparsely distributed in these two animals

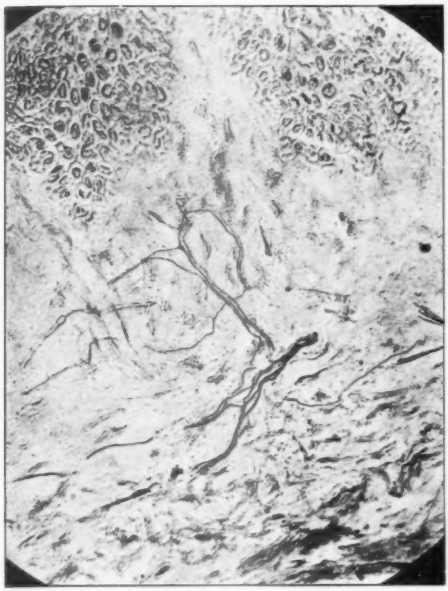

FIG. 2.

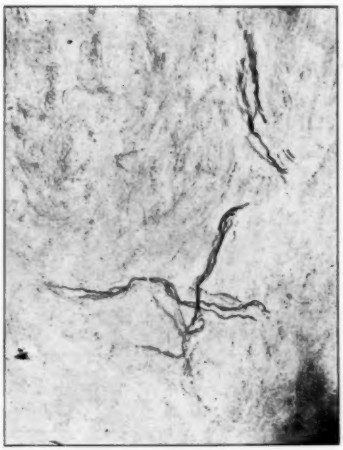

FIG. 3.

FIG. 2.—Superficial plexus showing true anastomosis of fibrillæ (Human).
FIG. 3.—Superficial plexus (Cat).

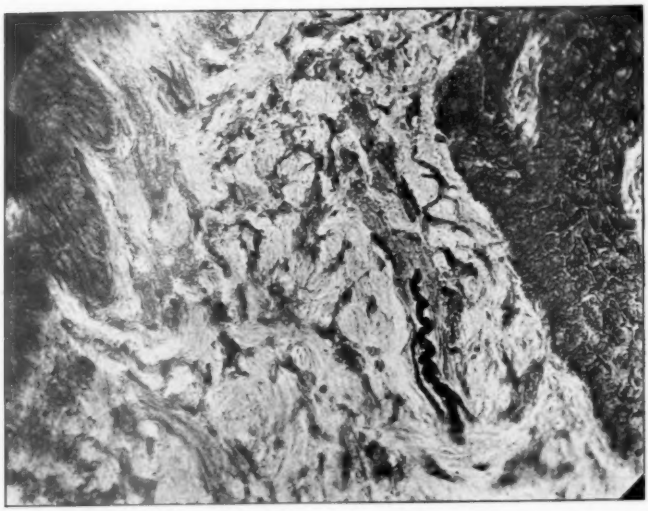

FIG. 4.—Subpapillary nerve-ending (Ferret) resembling Type 1 ending of the periodontal membrane of this animal.

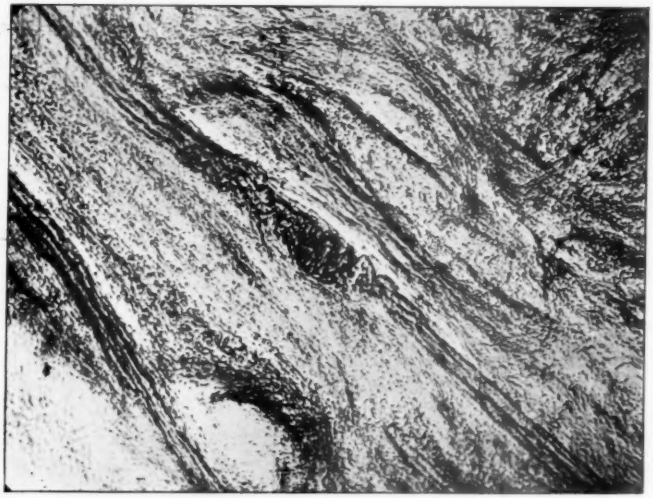

FIG. 5.—Complex convoluted nerve organ in deeper subpapillary region (Human).

FIG. 6.

FIG. 7.

FIG. 6.—Convoluted nerve fibres in relationship to the underlying muscles (Mouse).
FIG. 7.—Subpapillary encapsulated coil (Cat).

and we have been unable to find them in the other animals which we have examined.

In the intrapapillary region the most characteristic structures are coils. These were originally classified and described in the human by Kadanoff and they were afterwards reinvestigated and photographed by ourselves (1938*b*). They have been divided into loose and close coils. Drawing 1 is a camera lucida drawing of three adjoining sections of a papilla containing a loose coil and demonstrates clearly the arrangement of these structures, and in fig. 8 we have a photomicrograph of another human specimen in which an intra-epithelial fibre is also present. This intra-epithelial fibre is of interest as it runs for a considerable distance into the epithelium. From the knowledge we now have of the superficial plexus which we have just described we are doubtful whether the term " loose coil " is justified, and if it might not better be considered as an extension of the superficial plexus into the intrapapillary zone.

Camera lucida drawing of three adjacent sections of a papilla containing a loose coil (Human).

The loose coils are numerous in certain areas of the gum but they appear to be absent in others.

The characteristic end-organs in the intrapapillary tissues in man are the close coils (fig. 9). They are always situated in the tip of the papilla and are composed of thick and thin fibres which end in a rounded ball due to the fibres anastomosing with each other. This specimen is of further interest in that the tips of two adjoining papillæ lie in close proximity to each other, and each contains a close coil. These intrapapillary close coils have been seen in the mouse and the ferret. They lack, however, the characteristic complexity of the human close coils, and this is clearly demonstrated in fig. 10 from the ferret, where the simplicity of the structure is obvious as it takes the form of a comparatively simple loop. Thick and thin fibres are present, but we have seen specimens in this animal where the coils were formed only by thick fibres. In the human papilla we have recently seen a form of nerve-ending which differs completely from the coils which have already been described. This consists of a single fibre which takes origin in the subpapillary zone and enters

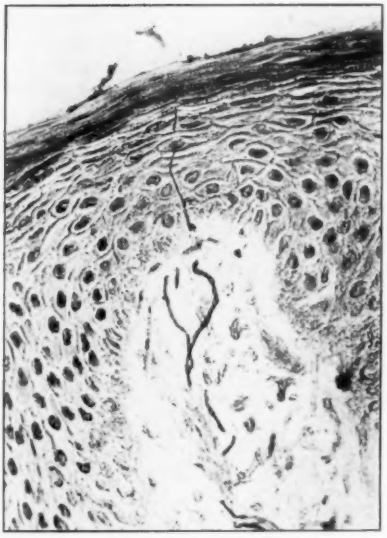

FIG. 8.

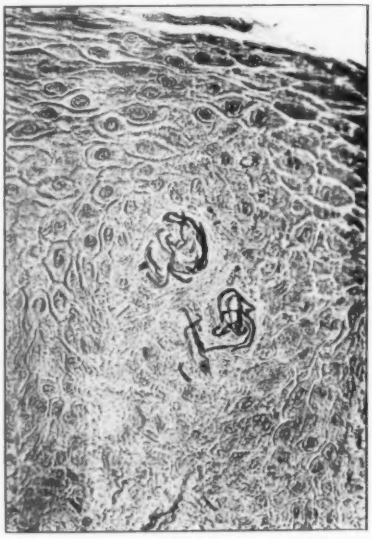

FIG. 9.

FIG. 8.—Loose coil with long intra-epithelial fibre (Human).
FIG. 9.—Two close coils lying in tip of two adjacent papillæ (Human).

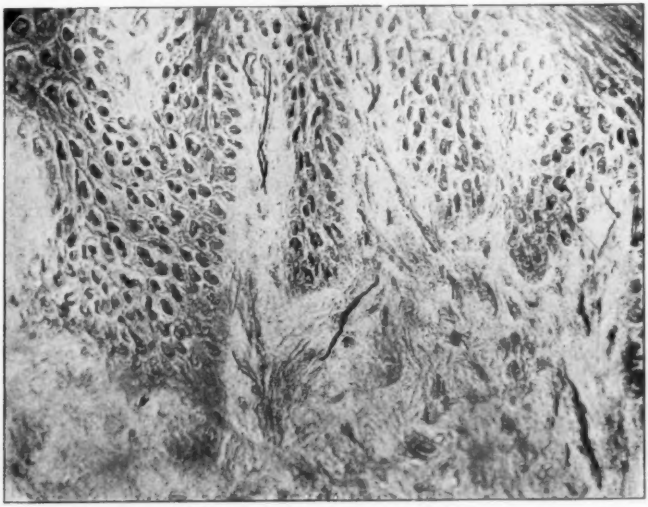

FIG. 10.—Coil of simple structure in tip of papilla (Ferret.).

the papilla to run for some distance within it. It finally ends in a definite bulb (fig. 11). There is no doubt that this slide shows the complete course of the fibre as there are no signs of any further branching in the adjoining sections.

As we have already mentioned, the connective tissue of the gum of the mole has a very rich nerve supply, as is clearly shown in fig. 12. Bundles of fibres will be seen running up from the deeper part of the connective tissue. In this animal we have found deep and superficial fibres, but we have been unable to discover any end-organs in the connective tissue. It is possible that this is due to the fact that there are highly specialized nerve-endings in the deeper part of the epithelial processes, namely the touch menisci described by Merkel and Ranvier (1880). An example of these

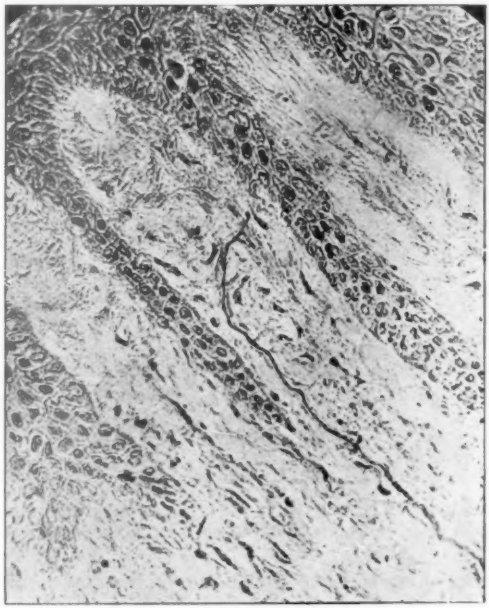

FIG. 11.—Single fibre ending in intrapapillary zone with a bulb-like swelling (Human).

can be seen in this specimen, but they are generally grouped together as terminations of nerve-fibres.

In conclusion, we have found deep and superficial plexuses in all the animals which we have examined. In the subpapillary layer of the carnivore there are present nerve-organs resembling the type 1 ending in the periodontal membrane of this order. In the cat, subpapillary coils were seen but no intrapapillary coils were found, whereas in the ferret intrapapillary coils *only* occurred. In the rodents we observed in the mouse subpapillary convoluted nerve-organs in contact with the underlying muscle layer which are very different from the spider-like ending seen in the periodontal membrane of this animal. Deep encapsulated and intrapapillary non-encapsulated coils were also seen in the mouse. In the rabbit intrapapillary coils were found, but we have not seen subpapillary coils, while in the rat subpapillary

and intrapapillary coils were present. In the mole no end-organs were detected ir the connective tissue of the gum. There were, however, specialized end-organs ir the deeper part of the epithelial processes—" the Merkel-Ranvier touch menisci." In the human we found a deeply situated subpapillary nerve-organ consisting of convoluted fibres which differed from the nerve-endings which we were able to find

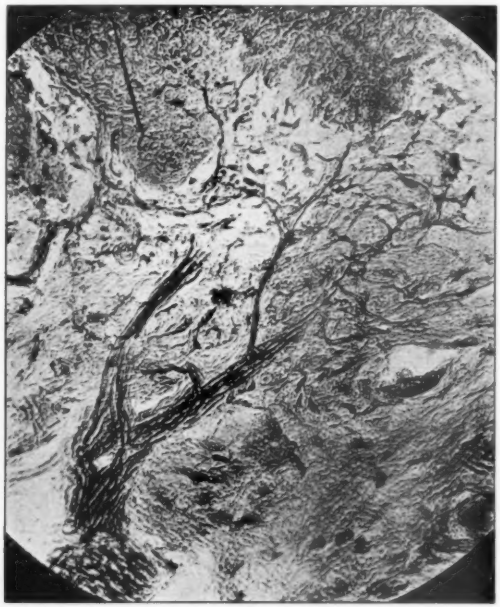

FIG. 12.—Distribution of nerve fibres in the gum of the mole with one Merkel touch disc (indicated by line).

in the periodontal membrane. No subpapillary coils were seen, but intrapapillary close and loose coils were found which differ in their complexity from the coils seen in the different animals. Another specialized intrapapillary nerve-ending was observed, consisting of a single fibre with a bulb-like swelling on the end which resembles the type 1 ending seen in the human periodontal membrane.

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Section of Medicine

President—H. L. Tidy, M.D.

[*March* 28, 1939]

DISCUSSION ON RECENT ADVANCES IN THE TREATMENT OF PNEUMONIA

Dr. L. E. H. Whitby: I propose to present the subject of recent advances in the treatment of pneumonia from the aspect with which I am most familiar, namely experiments in animals with chemotherapeutic substances.

The original experiments [1] with 2 (p.aminobenzenesulphonamido) pyridene, known variously as 2-sulphanilyl-aminopyridene, sulfapyridene in America, M & B 693 and the trade name of Dagenan, proved the efficiency of the drug against intraperitoneal infection in mice with types I, II, III, V, VII, and VIII pneumococcus. Since that time, whilst making comparative studies for the assessment of new synthetic compounds, the original work has been confirmed beyond doubt. This *in vivo* activity has also been confirmed by *in vitro* work by Fleming and his colleagues [2] with all 30 types of pneumococci. Fleming has found certain strains insensitive to the drug, and regards sensitivity as a factor of strain rather than of type. I have carried out a considerable amount of *in vitro* work [3] and have been impressed with the great care that must be exercised in arranging the experiments if consistent results are to be obtained. The sensitivity of the strain to the drug depends greatly on the phase of the organism, the age of the culture, and the degree of virulence. Unless these points are adhered to, and made standard, and checked by parallel *in vivo* tests, the results are unreliable. For instance, the virulent type I pneumococcus which I am accustomed to use for my *in vivo* work and of which something in the region of one organism constitutes a lethal dose, can be rendered avirulent by subculture, and is then quite insensitive to M & B 693 in an *in vitro* experiment. Rough and avirulent organisms are quite insensitive. Applying these results to clinical medicine one finds that M & B 693 is most dramatic and effective in acute infections, and that its action in chronic long-standing cases of bronchitis may be very little.

Clinical trial of M & B 693 was first made by Evans and Gaisford [4], and their good results have been confirmed by reports of small numbers of cases as well as of larger series from Africa [5] and America [6]. The results show clearly, in confirmation of experimental work, that the drug is not influenced by type and that provided the patient can live for twenty-four hours and can retain some 5 grm. of the drug, the chance of a successful issue is greatly increased—this irrespective of the day of the disease on which treatment is begun, which is of course in strong contrast to the requirements of serum therapy. The report of Flippin and his colleagues [6] on a series of 100 cases (which had a fatality rate of 4% and which includes eight bacteriæmi ccases, with only one death) contains two significant statements, namely "Several patients who had received large doses of serum without apparent effect were given

sulfapyridene and recovered " and " We instituted treatment in every case regardless of complications or the apparent terminal condition ". All this indicates that M & B 693 should be the first line of attack in a case of lobar pneumonia. Whether passive immunization with serum or active immunization with vaccine should be combined with the drug is a difficult question to decide. The combined method yields even better results in animals than does the drug alone, but in actual practice, by the time type has been determined or a vaccine made, the first twenty-four hours' dosage of M & B 693 will have given some indication as to its efficacy and the combined method need only be employed where necessary.

In general, the scheme of dosage suggested by Evans and Gaisford [4] has been followed, and this scheme has given good results, namely 4 to 5 grm. in the first twenty-four hours, followed by 3 grm. daily up to a total dosage of 25 grm. There have as yet been no extensive studies to show what blood concentration such a course induces, but it has been established that the drug, owing to its insolubility, is not regularly absorbed in different individuals, that in some individuals just as good a result is obtained with a blood concentration of free drug from 1 to 3 mgm.% as from 10 to 18 mgm.%. This suggests that in certain individuals a lower dosage than 25 grm. may be used, and indicates that estimations of blood concentration will probably be an essential part of control in treatment. Flippin and his colleagues found that cases treated late in the disease, from the fifth day onwards, required no more than 15 grm. to bring about a crisis and effect cure.

In England it is difficult to obtain sufficient clinical material in one centre for a properly controlled investigation. But where such material is available I would press for the performance of complete laboratory control and investigation. It would be important to determine the fatality rate in bacteriæmic cases, because bacteriæmia influences prognosis more than type and provides the best material for assessment. It would be important to do daily controls on blood concentration, first to get more information on minimal effective blood concentration and second to determine whether failures were due to poor absorption of the drug rather than to resistant and insensitive strains; the question of insensitivity would necessitate *in vitro* and *in vivo* tests on the strains isolated from cases that did not respond to treatment. It is well known that the drug in the blood exists partly as the active unchanged form and partly as the inactive acetylated form; the proportion in different individuals varies greatly. The significance of this individual reaction has not yet been assessed, but those who acetylate the drug readily may well be those who are resistant to treatment.

Evans and Gaisford have emphasized the importance of not stopping drug treatment as soon as a critical fall in temperature occurs; rather must one continue with the course for about five days. The same feature is clearly shown by all animal experiments, namely, that abandonment of the drug before a period of at least four days is always associated with an exacerbation, which, in animals, is afterwards difficult to control.

Other problems of dose have also been investigated in animals. In order to obtain consistent cure in mice inoculated intraperitoneally with 10,000 lethal doses of living pneumococci, it is necessary to give three doses of 30 to 40 mgm. in the first twenty-four hours, followed by one dose of 40 mgm. daily for several days. If the dose used throughout is 20 mgm. instead of 40 mgm. the mortality is quite high. Estimations of the concentration of the drug in the blood show clearly that this mortality occurs not because 40 mgm. causes a higher concentration than does 20 mgm., but because on account of insolubility and slow absorption, 40 mgm. provides a depot which maintains the blood level at a reasonable point throughout a whole twenty-four hours. With 20-mgm. doses the blood level at the end of twenty-four hours is below an effective level. One can achieve a high proportion of cures in mice with doses as low as 2 mgm. provided the drug is administered four-hourly, night and day (Table I).

TABLE I.—TO SHOW THE EFFICIENCY OF M & B 693 WHEN ADMINISTERED IN LARGE SINGLE DOSES OR IN SMALL DIVIDED DOSES.

(Lethal control with this inoculum (10,000 lethal doses) : 0·8–1·0 average survival days in all experiments.)

Method : (A) At time of inoculation, at seven hours and thereafter once a day for four days.
(B) At time of inoculation and thereafter four-hourly, night and day, for four days.

Method	Dose (mgm.)	Number of mice out of six, surviving 7 days	Average survival time (days)	Total dose (mgm.)
A	40	6	7·0	240
	10	0	2·7	60
	5	0	1·8	30
B	10	6	7·0	300
	5	5	6·8	150
	2	0	5·0	60

High doses of the drug are not, therefore, necessary to effect cure and increasing the dose beyond a certain point does not necessarily increase the blood concentration ; the increase in dose merely maintains the blood level for a longer time. I shall comment again on this important fact because it implies that a sustained minimal blood concentration is of more importance than obtaining high concentrations. *In vitro* experiments [3] clearly demonstrate that there is a quantitative relationship between drug concentration and the number of bacteria that can be destroyed. Thus, *in vitro*, a concentration of 16 mgm.% will destroy 15,000 bacteria, whilst a concentration of 4 mgm.% will destroy something of the order of 10 bacteria. But the fallacy of applying this principle to clinical medicine, by which I mean the giving of small doses to relatively mild infections and large doses to desperate infections, is shown clearly by *in vivo* animal experiment. With an *in vivo* experiment it is necessary to give almost as much drug to cure an inoculum of 10 lethal doses as it is to cure one of 10,000 lethal doses (Table II). It is inconceivable that in human medicine there should exist clinical states which are caused by organisms numbering mere tens ; one would always anticipate thousands or millions.

TABLE II.—TO SHOW RELATION BETWEEN DOSE OF M & B 693 AND NUMBER OF BACTERIA.

Dose	Number of bacteria	Number of mice out of six, surviving 7 days	Average survival time (days)
40 mgm.	10^6	4	6·6
40 mgm.	10^4	5	6·6
40 mgm.	10^2	6	7·0
40 mgm.	10	6	7·0
40 mgm.	1	6	7·0
10 mgm.	10^6	0	3·0
10 mgm.	10^4	0	2·6
10 mgm.	10^2	2	4·3
10 mgm.	10	2	4·5
10 mgm.	1	6	7·0
Control	10^4	0	0·8
	10^2	0	1·0
No drug	10	1	2·0
	1	3	4·0

I make this point because of the tendency, which exists in the profession, to use small doses in relatively mild infections or to give only a few doses. The basic indications for the use of this drug are clear, namely the occurrence of definite coccal infection ; it is not a specific for every fever of unknown origin, and so far as I am aware it has no action in influenza unless there is secondary coccal infection. When the drug is used it should be used in full doses and for the full ordinary course.

The disadvantage of M & B 693 lies not in the rare serious complications which are common to all the sulphonamide group, namely, grave blood changes, and these must be relatively rare considering the pounds if not tons of the drug that have been

used and abused in the past six months. The main disadvantage is that in some 30% of ill persons it acts as a gastric irritant causing vomiting, which is sometimes alarming. Often the vomiting subsides within twenty-four hours and the drug can then be continued, while various methods of administration, e.g. powdering, suspending in milk, fruit juice, or administering in smaller doses at more frequent intervals, can be used to tide over the initial ill phases. On account of this disadvantage of gastric irritation, search has naturally been made for a soluble preparation suitable for parenteral use, and considerable attention has been paid to the very soluble sodium salt, which has been carefully studied from the laboratory aspect before being released for the clinical trial which it is now undergoing. The laboratory studies emphasize certain principles which must be borne in mind when using this preparation in the human subject. This sodium salt of 2-sulphanilyl-aminopyridene is highly soluble; a 33% solution is readily prepared so that an ampoule of 3 c.c. contains 1 grm; it has the disadvantage of having a pH of about 11, but when suitably diluted can be given even by the intravenous route; it is also, when diluted to about 2%, suitable for rectal administration and is fairly quickly absorbed. Because of its solubility it is also rapidly excreted. The maintenance of a constant effective blood concentration must involve multiple injections by night as well as by day. The history of the laboratory assessment of this drug will make this point clear. For some years I have been assessing the activity of new synthetic compounds by a routine method which has in the main given very satisfactory results. It involves the administration of the test drug at the time of inoculation, about seven hours after inoculation and then again once a day for several days. When sodium 2-sulphanilyl-aminopyridene was administered in this way, in the maximum tolerated doses, its activity was, relative to the insoluble parent substance, very small. The reason for this was soon clear when it was found that within a few hours of administration there was no drug at all in the blood-stream; it had all been excreted. Further investigations showed that after administration of the drug a high blood concentration, even a dangerously high one, was rapidly attained. Acting on these facts it was decided to re-assess the drug in small doses given at intervals of four hours, night and day—a laborious process—but one which demonstrated clearly the efficacy of this substance if properly used (Table III).

TABLE III.—ASSESSMENT OF EFFICIENCY OF SODIUM 2-SULPHANILYL-AMINOPYRIDENE (T. 837)

(Lethal control with this inoculum (10,000 lethal doses) 0·8–1·0 average survival days in all experiments.)

Method : (A) At time of inoculation, at seven hours, and thereafter once a day for four days.
(B) At time of inoculation, at seven hours, and thereafter twice daily for four days.
(C) At time of inoculation and thereafter four-hourly, night and day for four days.
(D) At time of inoculation and four-hourly for one day only.

Method	Dose (mgm.)	Number of mice out of six, surviving 7 days	Average survival time (days)
A	5	0	2·0
	10	0	2·2
B	5	0	3·7
	10	0	4·7
C	2	3	6·3
	5	6	7·0
D	5	0	2·5

Clearly the optimum dose, the spacing of doses, and the administration of this soluble drug to the human subject will require to be worked out carefully. One would anticipate that multiple injections of small amounts will be necessary. One might

forecast that the main use of this drug will be to tide over the first twenty-four hours, after which the effect, if any, should be followed by oral administration of M & B 693, in order to maintain a proper blood concentration for the requisite time. It is important to note that once a critical fall in temperature has been attained the occurrence of vomiting with the oral compound is much less frequent. It seems unlikely that the soluble salt will entirely replace the ordinary M & B 693.

In conclusion I shall summarize what, from the experimental aspect, appear to me to be important principles for the use of this powerful antipneumococcal and indeed antistreptococcal and even antistaphylococcal remedy. They are as follows :—

(1) A good result is to be anticipated more in acute infections than in chronic.

(2) The maintenance of a steady, safe, and effective blood concentration, is more important than the attainment of high levels, while levels which fluctuate below minimal effective concentration are liable to be inefficient.

(3) Minor coccal infections require the same dosage for cure as do heavier infections. If, therefore, the drug is to be used, it should be used in full dose.

(4) Soluble preparations, and this applies to all soluble sulphonamide derivatives, are quickly absorbed and excreted. The maintenance of an adequate blood level with a soluble preparation requires to be carefully controlled.

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Dr. G. J. Langley: Speaking as a clinician I know of no disease of which the first aphorism of Hippocrates is more fully true than of pneumonia. Experience is fallacious and judgment most certainly very difficult.

William Withering, at the outset of his original discourse on digitalis, remarked how much more easily one could write of a disease than of a remedy, and anyone who has tried to establish the facts of treatment, even in a clear-cut and common disease like pneumonia, will agree.

My contribution to this subject must concern itself with the serum treatment of the disease, much of which has already appeared in print from time to time during this past five years. The final figures, opinions, and results have slowly evolved over that period.

The importance of uniformity in any large series of cases can hardly be overestimated ; the whole of the cases reported now have been derived from the working community of the city of Salford. They have all been treated in two special urgency wards of the Municipal Hospital, to which patients outside the city are not admitted. The whole work has been done by three colleagues working in happy combination, the Resident Medical Officer, the Assistant Pathologist, and the Visiting Physician. The cases have been received from the outside practitioners and the proportion of cases admitted before the end of the third day of disease would argue a high grade of efficiency.

The cases studied have been strictly limited to the age-group 16 to 60, and outside this limit in either direction we record nothing of pneumonia cases in this hospital.

Much effort has been expended in making the diagnosis of the disease as accurate as possible, both as regards the disease itself and as regards the causative organism. If the diagnosis be in doubt then the results of treatment are in still greater doubt. The precautions taken have been : careful clinical history ; repeated examination

by at least two observers ; X-ray of the chest ; bacteriological examination of both blood and sputum ; typing of the organism ; review of the whole case when terminated ; post-mortem examination whenever possible. Records are maintained week by week and are not allowed to accumulate, with consequent gaps in the available information.

The general treatment of the patients has been uniform throughout ; oxygen when required has been given by nasal catheter and a Wolff bottle. For sedatives medinal, paraldehyde, and morphia have been used as required. Ample glucose in a fluid diet has been pressed upon the patient and a very liberal supply of fresh air in the wards has always been maintained.

Serum has been administered in large doses by the intravenous route to all patients who (*a*) were admitted before the end of the third day of the disease and who (*b*) showed the presence of pneumococcus types I or II. So far all the serum used has been British. Unless the serum treatment could be started before the end of the third day of the disease, it was never used. This entailed a complete clinical and bacteriological diagnosis within the time limit set.

To form a control series, those cases admitted after the end of the third day of disease have been used ; and this has caused considerable misgiving to the minds of the statisticians. The average duration of the disease on admission to hospital of the serum-treated group is two to three days, while that of the non-serum-treated group is four to nine days. It therefore remains to estimate the life-saving value of two and a half extra days in hospital. Had a true alternate case control been used in this work these objections had not been present, but the number of cases treated would have been halved and even now, after seven years of work, the numbers are too small for real significance. The important part played by age in the outcome of pneumonia is so widely recognized that any omission of this factor makes an opinion upon results almost impossible.

I regret that these tables cannot be read direct because of various disturbing factors which call for some comment. The factor of age is all too clear for those of us over the 40 mark, but what may be the factor which allows so large a proportion of those under 40 to reach hospital before the end of the third day of disease and yet makes so large a number of those over 40 to arrive after the third day ?

To prove that this is not a selection within the hospital administration, the times of admission of the higher type cases have been worked out and reveal the same fact. How far would physicians of experience agree with me that the early diagnosis of pneumonia is very much easier in patients under 40 than in those over that age ? There are obviously many added factors arising at an age nearer to 60 than arise at 25. A review of the Ministry of Health Reports and the relation of notified pneumonias to deaths from that cause serves to emphasize the importance of this subject, and these are the only really large figures available in this country.

The introduction about a year ago of diagnostic sera for the higher types of pneumococcus presented an opportunity for the further study of that mixed bag formerly referred to as group IV. It also involved pathologists in a great deal of extra work. So far we have made but little progress. Out of 38 cases investigated 12 failed to type at all, and of the remaining 26 we found 17 to fall within the types IV to VIII.

At the moment it appears true that we are unaware of the relative frequency of any of these higher types in this country and consequently we are unaware of the clinical course they are likely to run, and a great deal of laborious work lies ahead to make the necessary clinical and pathological observations. The outstanding lethal effect of type III pneumonia leaves one wondering whether another equally lethal type may yet be lurking about. At the same time as higher typing sera became available for clinical use M & B 693 was also introduced, together with experimental evidence, and some clinical evidence soon arrived to show that the drug was probably

apable of modifying the course of lobar pneumonia in at least some cases. The here clinical diagnosis of the disease is quite capable of offering very great difficulty, ut in the future this will be very greatly increased when the drug has been given early n the disease. In fact it may well prove difficult or even impossible to determine ow far the drug has been active in aborting a true pneumonia ; and how far it as been given, and results claimed, when the diagnosis had not been adequately stablished.

So far the drug has been used in our service and in the manner prescribed in 34 ases with three deaths and severe vomiting in 13 instances. It has been given only n the types I and II cases admitted after the end of the third day and in type III. Of its success or failure it is impossible to speak, but one point is of great interest : n the past eight years we have identified only nine cases of type III pneumonia, all f whom have died. Recently three cases have occurred and have been treated with the drug, and all three have recovered ; the first recoveries from this type of pneumonia which I have ever seen. It is true that two out of the three cases were under 30, and that during last week another case of type III arose which unfortunately died in spite of the drug, but the primary fact remains.

It is hoped that the reason for limiting the use of the drug in the manner indicated is clear. Unless it is possible to study the higher-type pneumonias in their course under expectant treatment, it will remain impossible to judge the effect of any treatment ; in fact we shall permanently lack controls. The combined higher types usually constituted about 25% of the total pneumonias, but in U.S.A. only V, VII, and VIII are responsible for more than 5% of cases, so that it will be necessary to classify and study 2,000 cases of pneumonia before the clinical course of any member of the higher group can be established in 100 cases, and this sounds very like crying for the moon in that it has occupied eight years to collect 1,200 cases.

It has been shown that an attack of pneumonia followed by recovery usually leaves the patient a carrier for about a month ; recovery of the type organism becoming more and more difficult with the lapse of time. I have very little evidence which makes me anxious to know whether treatment with M & B 693 has any effect upon the recovery of the organism from the sputum. Any information on this point would be most welcome, for it is obvious that if the pneumococcus is caused to disappear, bacteriological diagnosis becomes impossible thereafter, and we may find ourselves anxious to withdraw that old and hitherto true dictum—" happy is the physician who sees the patient last ".

The criticisms which have appeared in the American press and which were reviewed in the last number of the *Lancet* (1939 (i), 703) must have received considerable attention, and it may be well to remember the many years of work and labour contributed by our cousins and the high grade of efficiency to which they have attained in State serum treatment. The type of statistical criticism to which serum work has been subjected will call for a quite similar investigation of results attained by this drug, and it is for this that the American workers are asking in all fairness.

PNEUMONIA STUDIES.

Type	Age	With serum		Without serum	
		Recovered	Died	Recovered	Died
1	16–39	98	4	125	15
	40–60	33	6	57	12
2	16–39	46	3	44	6
	40–60	20	5	45	22

Group IV. Higher Types.

	Before end of third day		After the third day	
	Recovered	Died	Recovered	Died
16–39	46	4	55	6
40–60	21	9	35	22

Results of the Treatment of 400 Cases of Lobar Pneumonia with M & B 693

By Wilfrid F. Gaisford, M.D., M.R.C.P.

Physician to Dudley Road Hospital, Birmingham

In a previous publication (1938) Dr. Evans and I reported our results after three months' trial of M & B 693 in cases of lobar pneumonia. 100 cases had then been treated and in the succeeding nine months another 300 cases have been added to these.

Altogether nearly 700 cases of respiratory infection have been treated with M & B 693 at Dudley Road Hospital, Birmingham, since March 1938, and the following is a brief account of our results with the 400 cases of lobar pneumonia included therein.

It was appreciated by Dr. Evans and myself that our paper was only a preliminary one and that it was unwise to draw any conclusions from such a small series of cases, particularly in a disease like pneumonia in which one often encounters a run of a score or more cases with no fatalities. Furthermore, we had used the drug over such a limited period of time and that time April, May, and June, which might have coincided with a mild type of infection.

It is true that we were able to rule out the last because our control cases showed a mortality of 27% compared with 8% in the treated cases. We had only three types of pneumococci for determining which was the infecting organism, all others being included as group IV, and we made no investigations into the blood concentration of the drug or its mode or rate of excretion.

Since October the thirty types have been used and typing of the pneumococci in the sputum has been undertaken whenever possible. X-rays have been employed as a routine during this time instead of just in doubtful cases as at first. The diagnosis "lobar pneumonia" has been based throughout on the same essentials as originally, viz. a history of sudden onset, rigor or vomiting, fever, pain in the side of the chest, cough, often with rusty sputum, and physical signs of consolidation in the lung.

No attempt has been made to divide the cases into "mild" and "severe", and admittedly most of the former would have recovered in any case, but for fair comparison the hospital figures for the preceding two years are offered. The patients have been drawn from the same sources and treated by the same physicians using identical criteria of diagnosis throughout.

Children under the age of 5 are not included so as to avoid any controversial differential diagnoses between broncho- and lobar pneumonia and because they form a fitting subject for separate consideration.

Also excluded, both from the 1936 and 1937 cases and the M & B 693 treated ones, are patients dying within twelve hours of admission, of which there were 10 in 1936, 10 in 1937, and 4 in the treated cases.

This means that any patient, even *in extremis* on admission, who had a minimum of 3 doses of M & B 693, is included.

During 1938 M & B 693 was not used as a routine throughout the hospital till August, and 335 patients with lobar pneumonia did not have any, and 79 of them died (excluding 5 dying within twelve hours)—a mortality of 23·6%. This figure is in keeping with the 1936 and 1937 figures shown in Table I.

It will be seen that the number of cases in the various age-periods are fairly comparable and the drop in mortality is marked at all ages, except over 70. The second table shows this and the graph depicts the fall below and above the age of 50. (The figures refer to the number of cases.)

It has been in older patients that M & B 693 has seemed to give the most striking results. Patients with diabetes, chronic bronchitis, arteriosclerosis, or emphysema, have responded in a remarkable manner.

The mortality under 50 has fallen from 16·5% to 1·6%, and over 50 from 51%

TABLE I.

Age-periods	1936 Number of cases	1936 Deaths	1937 Number of cases	1937 Deaths	M & B 693 Number of cases	M & B 693 Deaths
5–20	127	5	153	7	115	0
20–30	71	11	72	11	72	1
30–40	78	15	91	21	76	1
40–50	67	27	67	22	51	3
50–60	44	19	56	26	52	8
60–70	24	13	18	11	25	9
Over 70	4	3	4	2	9	4
Total	415	93	461	100	400	26
Mortality	22·4%		21·7%		6·5%	

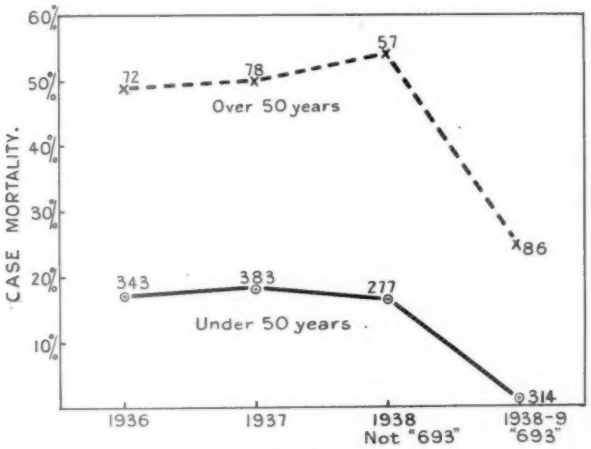

FIG. 1.

to 24·4%. The cases over 70 are not shown in the second table or in the graph as they were too few to be of significance—4 in 1936 and 1937 and 9 in the treated series.

TABLE II.—CASE MORTALITY.

Age-periods	1936	1937	1938	M & B 693
5–20	4	4	3·1	0
20–30	15·5	15·5	17	1·4
30–40	20	23	17·5	1·3
40–50	40	32·8	37	5·9
50–60	43	46·4	60	15·5
60–70	54	61	48	36

Table III shows briefly details of the 26 fatal cases. Those which are starred are ones on which post-mortems were held, just over half of them.

Seven of them were reported amongst our first 100 cases and the first five admittedly had insufficient dosage—no more than we give to an infant now.

Most of the others, as will be seen, had some complication or other.

The types are known in eleven (and two of the first five were group IV); one was a Friedländer and one grew nothing (No. 8).

These deaths refer to the pneumococcal lobar pneumonias only. We have had three deaths from staphylococcal (one of which was included in our first 100 cases but is excluded here), and two from streptococcal pneumonias and one diagnosed as a right upper lobe pneumonia who showed no response to M & B 693 was found at

*6	M	62	Type VIII. Chronic bronchitis and bronchiectasis.
*7	F	70	Type I. Recovered from pneumonia. Died from pulmonary thrombosis a week later.
*8	M	71	Whole of right lung solid. No pneumococci recovered from mouse inoculated with lung juice.
*9	F	39	Type II. Staphylococcal empyema.
10	M	67	Chronic bronchitis. Died within 36 hours. Left lower lobe solid.
11	M	52	Right lower lobe solid.
*12	M	63	Friedländer's bacillus from mouse inoculation of lung juice, bronchiectasis.
13	M	62	Type XVII in clear effusion at right base.
*14	M	69	Type I. RUL and RLL solid. Synpneumonic empyema.
15	M	61	Bronchiectasis. Right lower lobe solid.
*16	M	72	Type XXIII. Right lower lobe solid. Chronic bronchitis.
*17	M	64	Type I. Right lower lobe solid. Chronic bronchitis.
18	M	53	Died within 15 hours.
*19	M	54	Died in 19 hours.
20	M	68	Type I. Died in 21 hours.
21	M	77	Right lower lobe solid.
22	M	41	Died in 36 hours. Both lower lobes solid.
23	M	53	Hyperpiesis. Both lower lobes solid.
*24	M	55	Type I. Whole left lung solid.
25	M	55	Type X. Early empyema right base. Whole right lung solid.
*26	M	27	Type I in sputum and cerebrospinal fluid. Died within 36 hours.

H. influenzæ infections. There is a boy in one of my wards now, however, who is spitting up tubercle bacilli. He came in with a right lower lobe pneumonia (type XXIV) and responded well as regards his pneumonia to M & B 693 treatment.

It is almost certain that some of the 1936 and 1937 deaths were streptococcal or staphylococcal, but I have not been able to find out the exact number because our attention was not focused at that time on the bacteriology of our pneumonias.

By comparison with the later cases, if we allow that 2% were non-pneumococcal that would bring the figures into line. It makes the 1936 mortality 21% and the 1937 20% to compare with 6·5% in the treated cases.

The Effects of the Drug.

First on the temperature. We have found in nearly all cases a prompt drop to normal within forty-eight hours of starting treatment, irrespective of the day of the disease. Continued pyrexia after the full course of M & B 693 has indicated either the presence of some complication or more frequently, that the infecting organism is not a pneumococcus.

Second on the physical signs. I have not been able to determine any alteration in the rate of resolution : in some cases it seems actually to have been delayed though not to any marked extent.

Third on the patient. A gradual yet fairly rapid improvement takes place in the general condition following the fall in temperature, not so striking as at the normal crisis, but nevertheless clearly evident. The mental depression which is a characteristic sequela of the sulphanilamide group generally has been observed in a number of cases but persists for a very short while.

Complications of the Disease.

In addition to the six empyemas we had in our first 100 cases there have been 12 others, one staphylococcal (who had type I pneumococci in the sputum) and 11 pneumococcal, 10 type I and one type II, this predominance of type I being in accord with other peoples' findings. There were also two synpneumonic empyemas who died ; both type I.

In addition we have had four cases of clear sterile effusions, presumably aborted empyemas, which have delayed convalescence considerably. Another clear effusion was found at autopsy in a type XVII pneumonia.

X-rays showed fluid at the base in two more cases but spontaneous absorption occurred.

In the 461 cases in 1937 there were 30 empyemas, so the incidence does not appear to have increased, as we at first thought it might.

Complications of the Drug.

Possibly because our experience is still very limited, possibly because we have been lucky, our complications have only been minor ones. For example we have had no cases of anæmia or granulopenia and have found no evidence of kidney or liver damage either during life or at post-mortem. This applies not only to the 400 cases under discussion but to all the patients who have received M & B 693.

We had the opportunity of seeing one case at autopsy six months after he had recovered from pneumonia—having died after falling downstairs—and an extensive examination by Dr. Whitelaw, the hospital pathologist, failed to reveal any evidence of residual toxic effects.

Seeing that all the drug is excreted—at least from the blood and urine—within forty-eight hours of discontinuing treatment, this is not surprising.

We have, of course, seen a number of rashes, and these have been similar in character to the sulphanilamide rash though less severe, and in allergic patients have forsaken the usual morbilliform type and become frankly urticarial.

Commonly the rash arises during treatment, but may be delayed till two or three days after treatment has ceased. It is independent of the amount of drug given and disappears in the course of a few days.

Cyanosis.—We still see this in a number of cases, but it has ceased to be a worrying sign. It disappears promptly, like the rash, when treatment is discontinued. Cyanosis already existing is not a contra-indication to prescribing M & B 693 and may be treated by oxygen or venesection in the usual manner.

Vomiting.—In babies and young children vomiting after M & B 693 is practically non-existent. Unfortunately, as everyone has found, such is not the case among adults.

In view of the fact that we believe that large initial doses give the best results this vomiting becomes an important consideration. It is sometimes extremely difficult to overcome. Occasionally it is psychological but more often dependent on the presence of gastritis, either due to the infection, or pre-existing. It is not of central origin, nor is it due to variations in the tablets as we at first thought might be the case, as these now consist of the pure drug in compressed form and contain no acid extractive as did those we used originally.

Some patients undoubtedly take the tablets better when they are crushed and suspended in water or hot or cold milk ; others can swallow them whole without upset. If coughing causes vomiting they may be given suspended in a linctus.

When vomiting does occur the next dose should be given by a different method, e.g. if vomited when given whole they should be crushed and suspended next time.

Some patients can take smaller doses, e.g. one tablet at hourly intervals, and this method is worth trying if the others fail.

It has been my experience that only rarely is the vomiting so persistent that ar.

insufficient amount of the drug is retained, but in such cases a parenteral method of administration is desirable.

We have for some weeks past now been using solutions of the sodium salt of M & B 693 both by intravenous and intramuscular injections.

It is too early yet to give details of our investigations and findings, but I can say that while the intravenous results are not yet satisfactory the intramuscular route has proved highly so, being free from reaction, not giving rise to vomiting, no more toxic than M & B 693 given orally, and producing results as good or better. We have not yet determined what strength solution, dose, or interval, is optimal. We are investigating the blood concentrations attained and the rate and mode of excretion, but it will be some time before our results will be ready for publication.

Dosage.—In general we adhere to our originally suggested dose of four tablets (2 grm.) on admission and two tablets four-hourly thereafter till the temperature falls, and then one thrice daily for twenty-four to forty-eight hours. This last is to obviate the secondary rise of temperature which occurs if treatment be stopped too soon and which has been shown to be due to a direct spread of the disease process in the affected lobe.

In milder cases two tablets four-hourly will usually suffice, while in severe cases I give four tablets four-hourly for four doses, giving 8 grm. in the first twelve hours after admission and then continue with two tablets four-hourly.

This saturation of the system in the first few hours has the advantage of allowing what is often a much-needed sedative to be given, and subsequent doses are omitted till the patient rouses.

The non-specific treatment of these pneumonias has consisted in good nursing, as much fresh air as possible, fluids freely, frequent mouth-washes, adequate attention to the bowels, Gee's linctus, and morphia after the intensive treatment is finished if sleeplessness is a worrying symptom.

Typing.—Typing of the pneumococci from the sputum has been done in rather more than half the cases but, as has been said, we have been using the 30 types only since October, so our figures are still too small to be of great value.

Dr. Whitelaw reported that he was unable to assign any type number to some of the specimens he received, but Table IV shows such results as we have obtained to date. Lung puncture has not been employed.

TABLE IV.

Type	Number of cases	Deaths
I	94	6
II	27	1
III	28	0
IV	4	0
VI	3	0
VII	6	0
VIII	9	1
X	1	1
XII	1	0
XV	1	0
XVII	2	1
XVIII	2	0
XIX	1	0
XX	4	0
XXI	1	0
XXIII	1	1
XXIV	1	0
XXIX	2	0

To sum up, it may be said that M & B 693 represents a real advance in the treatment of lobar pneumonia, and the improvement in results is comparable with that seen in streptococcal infections since the introduction of sulphanilamide.

The drop in mortality which we experienced in the first three months of using this new drug has been maintained for a year, and we have found it to be almost completely non-toxic.

[I am indebted to Dr. F. W. Ellis, Medical Superintendent of the Hospital, for permission to publish these cases, to my colleagues for their collaboration, and to Dr. Whitelaw, who did all the autopsies and the typing of the pneumococci.]

Professor Alexander Fleming said that the aspect of the subject in which he was most interested was the combination of immunological methods with M & B 693. It was generally accepted that M & B 693 prevented the growth of, rather than killed, pneumococci in human blood, so that it was left for the natural defensive mechanism of the body to complete the destruction of the cocci, and if this mechanism was faulty then the result obtained by M & B 693 would be poor. It seemed an obvious corollary to this that the higher the degree of immunity of the patient the better would be the apparent result of the drug, and this inevitably leads to the conclusion that theoretically it should be good practice to increase the immunity of the patient as well as to give the drug. This theoretical consideration had been borne out *in vitro* and in laboratory animals, and to a certain extent by clinical experience, although this was as yet meagre. The combination of a specific serum with sulphanilamide had been shown to save mice which would inevitably have died from the infection had either the serum or the sulphanilamide been withheld. It had been shown also that a single dose of pneumococcus vaccine given a few days before infection saved mice treated with M & B 693. There was clinical evidence also that sulphanilamide or M & B 693 gave better results in patients whose immunity has been raised either as a result of the infection itself or as a result of vaccine treatment.

Throughout his life Professor Fleming's interest had been in active immunity by vaccines rather than passive immunity by serum, and he sincerely hoped that in the near future someone in a community where pneumonia is common would treat a series of patients with a combination of pneumococcus vaccine and M & B 693. He would look forward to such a series of observations showing that the 6% of failures with the drug alone being reduced to 1% or even less. Pneumonia did not give much time for active immunity by vaccines, but the experimental results indicated that a very small rise in immunity would, in combination with M & B 693, determine a favourable result. There was quite good evidence that in pneumonia patients a well-marked immunity response (probably far greater than would be effective in combination with M & B 693) is manifest in some three days after a single dose of pneumococcal vaccine. This being so there was every likelihood—although it had yet to be proven—that in a far shorter time sufficient immunity would have developed to have a marked result on pneumococci affected by the administration of M & B 693.

Some physicians believed in simple vaccine treatment of pneumonia, and there were some who have used it for many years as a routine procedure. The advent of M & B 693 seemed to him likely in the long run to greatly increase the number who adopt this method in combination with chemotherapy.

Another aspect of the subject which might have some bearing on the failures of treatment by M & B 693 was the acquired tolerance or fastness of pneumococci to the drug. Maclean, Rogers and Prof. Fleming himself had recently published evidence that pneumococci could, in animals, rapidly become tolerant to M & B 693. In the last few days they had been doing experiments with two cultures of pneumococci which were sent to them from New Guinea by Dr. Backhouse. These were both pneumococcus type I; the first was isolated from a patient just after M & B 693 treatment was commenced, and the second was isolated from the same patient 3¾ days afterwards at the post-mortem. During this time the patient had received 28·5 grm. of M & B 693. When they tested these two cultures for sensitivity to M & B 693 they found that the first was moderately sensitive but the second was extremely insen-

sitive. The simplest explanation of this case was that the patient did not have sufficient immunity to deal with the pneumococci even after they had been subject to a high concentration of M & B 693. The treatment therefore did not save the patient but it was evident that it immunized the pneumococci to the drug.

Dr. H. Stanley Banks said that in the Park Hospital recently about 30 cases of pneumonia in adults had been typed and treated with M & B 693. Types I, II, III, IV, VI, VII, VIII, X, XXI, and XXIII, were represented. The cases were mostly middle-aged or elderly persons. He had been impressed with the absence of mortality so far in this small series of unpromising prognosis. The sodium solution of the drug had been used intramuscularly to replace the oral administration of tablets when vomiting made it necessary. He thought that the sodium solution was less toxic than was at first supposed, and that it should be used in not less than half the dosage, weight for weight of that applicable to the tablets. The incidence of empyema in treated cases of pneumonia appeared high. He had found that the content of the drug in the pleural pus was frequently higher than that in the blood, and, in spite of this, the organism could be cultured day after day from the aspirated pus. This applied even when the diluted sodium solution was injected into the pleural cavity and the content of the drug therein maintained at very high levels such as 80 to 100 mgm.%. He asked Dr. Whitby if it were known that the pneumococcus might become insensitive to M & B 693 under these conditions.

Dr. Maurice Davidson said that, while the value of M & B 693 was universally admitted, it was desirable to make some protest against the indiscriminate use of this and other preparations of the sulphanilamide group. Apart from the fact that wholesale administration of such drugs in various febrile conditions, without a certain diagnosis and without scientific control, was wrong in principle, he felt that a risk might be entailed of damage to vital organs of the body. He would like to ask the chief speakers whether there was any evidence of delayed after-effect of M & B 693 and allied drugs, e.g. damage to the renal epithelium or to the myocardium.

Dr. Whitby in reply, said that the drug might well be ineffective in a medium such as pus. Laboratory experiments clearly showed that the action of these drugs was sometimes inhibited by the presence of certain proteins. With regard to Dr. Davidson's query, there was no evidence to this effect, no such delayed after-effect had now been reported.

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President—Air Commodore H. E. WHITTINGHAM, C.B.E., K.H.P., F.R.C.P.Ed.

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The Treatment of Malaria in a Military Population with the Synthetic Preparations

By Lieutenant-Colonel S. SMITH, F.R.C.P.

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IN seeking how best to approach this rather controversial subject, the uses and abuses of the new synthetic antimalarial remedies, I have decided to record only my own personal experiences with these drugs in the various military stations in India and in China in which I have served.

My remarks necessarily deal with a very limited and, in many respects, selected section of the population, namely, the British serving soldier and his officers, and any observations I shall make have, therefore, only reference to this specialized community.

I propose to relate my experiences in chronological sequence, dividing them into three periods, corresponding with my three tours of foreign service :—

(1) Quinine : 1919 – 1924 (India). (2) Plasmoquine : 1928 – 1932 (India). (3) Atebrin ; plasmoquine ; tebetren : 1936 – 1938 (Hong Kong).

The first tour of service was spent in the South of India, mostly in Poona and Secunderabad. In these two stations, especially the latter, I had ample opportunity of acquainting myself with both the merits and demerits of quinine, so potent and satisfactory in its action on the acute attack, so thoroughly ineffectual in preventing a high relapse rate. In addition, the prolonged treatment then in vogue, the bitter taste, almost impossible to hide, the unpleasant if non-mortal side-effects, and the by no means rare idiosyncrasy evinced by some to its use, even in the smallest doses, were very definite drawbacks.

During my second tour of service abroad I spent a year (March 1928–March 1929) as Medical Officer in Charge of the Malaria Treatment Centre, Kasauli, where I learned a good deal about plasmoquine and its effects.

The Malaria Treatment Centre was opened here early in 1924 in the hope of finding, from among the multitude of antimalarial drugs already on the market or projected, a really satisfactory treatment for chronic relapsing malaria, at that time by far the most crippling disease with which our Army in India had to cope.

Major, now Lieutenant-Colonel, J. A. Sinton, V.C., O.B.E., was its first commanding officer—a very happy choice, as he brought with him a very considerable experience of malaria in all its aspects.

Kasauli was chosen as the site for this new venture for many reasons, not the least important of which was that, at a height of 6,100 ft. above sea-level, it was above the malaria belt in that particular latitude, and the results obtained were therefore not vitiated or distorted by reinfection of susceptible individuals, and one could be sure that any second relapse that occurred at the M.T.C. was due to the inadequacy of the treatment there employed during the first relapse, and not due to reinfection.

The routine employed was briefly as follows (S. Smith, 1929) : Cases of chronic relapsing malaria (mostly B.T.) were transferred to Kasauli from the various military stations scattered throughout India. These individuals were, on arrival, if not at

the time suffering from a clinical relapse, accommodated in nearby barracks, and there they remained until such time as they again relapsed, when they were at once admitted to the treatment section of the Centre.

During this convalescent period they performed such fatigues and other duties as were required of them and attended weekly at the out-patient section for certain tests to be made. These comprised blood-film (thick smear) examination, spleen measurement, blood-counts and hæmoglobin estimation, blood-pressure and weight, all of which were recorded on special charts kept for the purpose.

Each case, as soon as he relapsed, was immediately transferred to the in-patient section, where he received, under rigid test conditions, the antimalarial drug or combination of drugs then under trial or alternatively the standard control quinine course.

Particulars as to daily parasite count, length of pyrexial period, daily spleen estimation, gain or loss of weight, effect of treatment on the blood-pressure, effect on the blood picture, &c., were again recorded on special charts.

By these means a good deal of specialized information concerning the action of the many drugs and combinations of drugs under trial was accumulated, and has been recorded by Sinton and his collaborators in a series of articles (1926, 1926*a*, 1927, 1928, 1930).

Prior to the introduction of plasmoquine, however, none of them compared in any way with quinine as an antimalarial remedy.

I joined the Malaria Treatment Centre early in 1928, when plasmoquine was under trial. Major Sinton had then taken up the appointment of Director of the Malarial Survey of India, with its headquarters also at Kasauli, but continued to act in an advisory capacity to the M.T.C. During my year's residence at Kasauli I grew to respect plasmoquine for its marked effect in lowering the relapse rate, but also, in some respects, to dislike it on account of its toxic action in any but the smallest doses. Its action as a gametocide, although of course known, had little local application, as we were not concerned, directly, with reinfections.

My predecessor had given the drug in doses as large as 0·1 grm. daily, and during the early part of my tenure we gave it in appreciably larger doses than is recommended nowadays, viz. 0·06 grm. daily, for twenty-one days, combined with quinine. Under this dosage, a high proportion of patients (over 60%) suffered from toxic manifestations, all of minor degree, which, however, necessitated an interruption of the treatment for several days. Cyanosis due to methæmoglobinæmia, and colic referred to the epigastrium were the two toxic symptoms complained of by the great majority of patients. One or both of these symptoms commonly occurred between the sixth and ninth days of treatment ; if plasmoquine were now withheld for a few days during which the quinine could be persevered with, the toxic manifestations rapidly disappeared, and, in most cases, the full plasmoquine course could then be completed without any return of symptoms.

Later, amongst a small group receiving 0·04 grm. of plasmoquine daily, in combination with quinine, only a small proportion (under 20%) exhibited toxic manifestations.

Amongst the considerable number of cases treated at the M.T.C. with plasmoquine, there were no examples during my time of severe intolerance to the drug, and all those who exhibited mild toxic symptoms recovered completely after a few days' withdrawal.

One case, however, sent up from the plains, where he had admittedly received a gross overdose of plasmoquine (due to a mistake in the position of the decimal point in prescribing the drug) nearly died soon after arrival. His chief symptoms were marked cyanosis, vomiting, severe epigastric pain, liver tenderness, jaundice, hæmoglobinuria. He subsequently had four relapses of malaria, and, as we dare not give him more plasmoquine, he was eventually invalided home.

This accident led me to emphasize the importance of paying great respect to the

orrect position of the decimal point in either prescribing or writing about these nodern synthetic remedies (S. Smith, 1929*a*).

The conclusion reached at the time I left the Malaria Treatment Centre, early in 1929, was that plasmoquine, in small dosage, 0·04 grm. daily [later reduced to 0·03 grm. daily] given continuously with quinine for twenty-one days, was the best treatment so far tested for benign tertian malaria, but that " the margin of safety between the therapeutic and toxic doses is so dangerously narrow that daily supervision is necessary in the case of patients undergoing treatment with plasmoquine ".

Early in 1932, whilst medical specialist at Rawalpindi, I received from Simla for trial a small supply of a new drug, erion (atebrin), to be given in tablet form *combined* with plasmoquine, the latter in the usual dose. My first impressions of this combination were bad, several cases exhibiting severe toxic symptoms, and the effect on the malarial attack was far from satisfactory.

It has, of course, been abundantly shown since, that these two drugs, if given in a combined course, should be administered *consecutively*, not *concurrently*, as, if given together, the toxic effects of each appear to be enhanced by the presence of the other.

This was my last experience with atebrin until I returned to the Far East, this time to Hong Kong in 1936. Up to and including the year 1935 the incidence of malaria at Hong Kong had not been high, averaging about 70 cases annually amongst a garrison of some 6,000. From 1936 onwards, however, the admission rate, largely as a result of greatly increased military activities, has more than trebled, and during the three years I was in the Colony I treated 651 cases of malaria with one or other of the new synthetic drugs.

My predecessor had, up to the time of my arrival in Hong Kong, been treating his cases of all forms of malaria with a combined course of atebrin and plasmoquine given concurrently, atebrin 0·1 grm. three times in the morning, plasmoquine 0·01 grm. three times in the evening, for six days ; followed by plasmoquine alone for a further five days. I must admit that his results appeared excellent—on paper. I did not see the cases under treatment as I only arrived shortly before he left, when malaria was at a low ebb and the relapse-rate was extremely low. The only disadvantage was this question of toxicity.

With my previous experience of the toxic effects of plasmoquine (especially when given concurrently with atebrin) still vivid in my mind, I gave, in the case of benign tertian and quartan infections only, an eight-day course of atebrin alone, reserving for malignant tertian cases a six-day course of atebrin, followed after a rest period of two days, by a five-day course of plasmoquine. This latter course, with one modification presently to be described, worked well, and I had no occasion to alter it.

The atebrin course adopted for benign tertian and quartan cases, whilst proving satisfactory as far as the individual malarial attack was concerned, quite failed to keep down relapses within reasonable limits, and we were faced with a relapse-rate in the region of 37%—reminiscent of the quinine era.

I therefore substituted the combined atebrin-plasmoquine course for all forms of malaria, which, previously, I had reserved for malignant tertian cases only. The result was an immediate drop in the relapse rate to under 6%.

From the middle of 1937 I have adopted this combined (or consecutive) atebrin-plasmoquine course for all forms of malaria, introducing latterly two important modifications.

Although at first quite satisfied with atebrin in so far as its action on the acute attack was concerned, latterly I have come to the conclusion, as indeed have others (Amy and Boyd, 1936*b*), that its action on the initial fever is notably slower than that of quinine.

To test this point, I treated a series of cases of benign tertian malaria with an initial two-days' course of quinine, switching over to the atebrin course at the end of this period. The effect of this change on the initial pyrexia was at once evident ; the duration of fever being reduced on an average by nearly one day as a direct result.

(Duration of fever after commencing with atebrin averaged 1·5 days; duration o fever after commencing with quinine averaged 0·6 day.)

During the summer months we had amongst our admissions for malignant tertian malaria a considerable proportion of serious cases, some few of which were o the grave cerebral type.

To add to our difficulties, several, who on first admission appeared to give n special grounds for anxiety, on the third or fourth day after admission became gravely ill, either collapsing with a subnormal temperature or, in one case, dying after a short bout of hyperpyrexia.

Post-mortem examination in two such cases revealed no large aggregation of malignant tertian parasites in the internal organs. In one case (collapse) the suprarenal bodies were found to contain small cortical hæmorrhages and areas of necrosis.

An excellent description of anomalous cases of this type with very similar post-mortem findings is to be found in the Official History of the War, Medical Services (1922).

With these unfortunate occurrences in our mind, and being impressed by the fact that there was nothing in their condition on admission to suggest they would develop these alarming symptoms, we have given latterly all cases admitted with malignant tertian malaria one to three intramuscular injections of atebrin musonate as a preliminary, at daily intervals, completing the six-day course with oral atebrin. A similar routine was carried out at the Royal Naval Hospital, Hong Kong.

We have, so far, treated some 50 cases of malignant tertian malaria with these initial intramuscular injections of atebrin musonate and have every reason to be satisfied, and I am convinced it is a life-saving measure. We had no bad results, local or general, attributable to atebrin, either given intramuscularly or orally.

On the whole, I prefer intramuscular atebrin to either intramuscular or intravenous quinine in the treatment of these malarial emergencies. Atebrin musonate may also be given as an intravenous injection but this route is not recommended by the manufacturers who maintain, probably correctly, that the absorption of this drug is almost as rapid by intramuscular as by intravenous injection, and less dangerous by the former route.

There was one disastrous period, luckily short, during 1938, when I departed from my practice of never giving atebrin and plasmoquine in actual combination, and gave, for a limited period, pellets of combined atebrin and plasmoquine (atebrin 0·1 grm.; plasmoquine 0·005 grm.) under the mistaken impression that plasmoquine, in this minute dosage, even when combined with atebrin, would have no ill-effect. Apparently I was wrong in this supposition, for whilst the majority of the cases thus treated gave no cause for anxiety and ran a normal course, one case of malignant tertian malaria died suddenly on the fifth day after admission; a second died eight days after admission; and yet a third developed severe agranulocytosis and only recovered after a stormy course.

The proportion of unfortunate occurrences in this small series of 12 cases appeared much too high to be entirely coincidental, so we stopped this combination treatment.

When to apply the therapeutic test of quinine or atebrin in undiagnosed but suspected malaria has always presented a difficult problem.

Formerly, I believed that, provided the patient remained in hospital under *constant medical supervision*, two blood slides (preferably thick films) at least being taken daily and examined at once by a competent observer, until a positive diagnosis is arrived at, one could, with some degree of safety, delay the exhibition of the specific antimalarial remedy until a positive blood slide was obtained. I have in the past delayed the commencement of specific treatment up to ten to twelve days in such cases.

Whilst admitting that this doctrine may still hold good where only benign tertian or quartan infections are met with, it is dangerous in districts like Hong Kong where severe malignant tertian infections are to be expected.

The danger of thus temporizing was shown by one unfortunate case :—

A bombardier was admitted to hospital from a very malarious district during the summer, complaining of malaise, slight irregular fever, and headache, which he said, he had had off and on for a month. His wife had been a hospital nurse, and although she denied having given him any drug other than aspirin, I suspect he must have had quinine prior to admission. For five days after admission he ran a high remittent fever with occasional rigors. The spleen was not palpable ; the temperature not of the alternating type, and blood-films, taken twice or thrice daily, were consistently negative. On the sixth day after admission a blood-film showed, for the first time, an exceedingly heavy infection with malignant tertian rings. His clinical condition at this time gave no special cause for anxiety and he was put on the standard atebrin course forthwith. In spite of energetic antimalarial treatment, however, he died three days later.

Autopsy revealed a moderate degree of malarial pigment in the spleen and brain capillaries but no large aggregation of parasites in any of the internal organs.

Later, another complicating factor arose, in that most of our cases had received, prior to admission, prophylactic quinine—that bugbear of the clinician and clinical pathologist—and positive blood slides became the exception rather than the rule. In my annual medical report for 1938 I noted that " Difficulty was experienced during the latter three months of the year in obtaining positive blood slides owing to the fact that the Artillery at Lymun and the Battalion at San Wai Camp, in the New Territories, were on prophylactic quinine prior to their admission to hospital. On this account there was from these two units, especially the latter, a high proportion of cases diagnosed as ' clinical malaria ', who, on clinical grounds, were almost certainly suffering from malaria, but in whom blood slides examined twice daily, were consistently negative.

" An average of three days elapsed before positive blood slides were obtained in the case of those who had been on prophylactic quinine prior to admission ; whereas in the case of those who had not been on prophylactic quinine positive slides were obtained on an average in 1·5 days. Also, the incidence of clinical malaria was much heavier amongst those who had been on prophylactic quinine."

Of a total of 228 admissions for malaria during 1938, when prophylactic quinine was in vogue, 32 were classified as clinical malaria, the great majority coming from amongst the two units which were on prophylactic quinine, whereas amongst a total admission rate of 211 during 1937, when some units were on prophylactic atebrin, but *none* on quinine, there was only one diagnosed clinical malaria, and he had not been on any form of prophylactic treatment prior to admission.

One must admit that the results obtained with either form of prophylactic treatment were far from conclusive.

It is for cases such as the above that one might hope to obtain some help from such non-specific tests as the melano-flocculation test of Henry or the recent colorimetric modification of this test devised by H. O. Proske and R. B. Watson.

In these circumstances we decided, somewhat reluctantly, to give all cases admitted during the malaria season, and exhibiting fever which did not respond rapidly to symptomatic treatment, some form of antimalarial therapy, preferably atebrin. We preferred atebrin to quinine because it appears to have a provocative action not possessed by quinine, and parasites are often found in the peripheral blood for the first time after a few doses of atebrin.

Tebetren.—This antimalarial remedy was sent us by the War Office for trial as an alternative to atebrin and plasmoquine, both of which might, in certain eventualities, become non-available.

Tebetren is stated by the makers, a British firm of manufacturing chemists, to be a combination of acridine and quinine derivatives together with a derivative of cholic acid to act as a detoxicating agent.

Favourable reports concerning its action, both on the acute attack and on the relapse-rate, are reported by D. G. Stoute (1932) and Barrowman (1933).

The drug is said to be cumulative in its action, and both these authors report a proportion of toxic side effects in their cases, Barrowman stating that the " margin between the therapeutic and noxious doses is small ".

We were only sent a limited supply, insufficient for extended trials, and we were unable to supplement our stock from local supplies, the drug being unprocurable in Hong Kong.

We used it almost exclusively in benign tertian infections, and its action on the acute attack was almost identical with that of atebrin. The relapse-rate following its use was also somewhat high, about 36% amongst cases treated with the drug during 1937, again about the same as with atebrin. We had a lower relapse rate of approximately 17·6% with a second batch of cases treated during 1938 (this does not take into account, however, the spring relapses, which will undoubtedly materially raise this figure).

In the small dosage we employed—6 gr. three times daily for eight days—we had no ill-effects.

I have no personal experience of the new antimalarial remedy, certuna, which, according to its discoverer Kikuth, is superior in its action to plasmoquine, in that it is gametocidal without producing the toxic manifestations of the latter.

Of the synthetic remedies I have mentioned, therefore, we have in atebrin a drug which has an excellent and rapid effect on the acute attack, especially if reinforced by quinine, rapidly frees the peripheral blood of parasites, is almost non-toxic, and is not unpleasant to take. On the other hand, it is little, if any, better than quinine in reducing the relapse-rate in benign tertian malaria, and it has little or no action on the gametocyte (crescent) stage of malignant tertian malaria.

Plasmoquine, on the other hand, has a relatively poor effect on the acute (trophozoite) stage of the disease, and is seldom used alone, for this reason : it is very toxic in all but the smallest doses, and many have an idiosyncrasy even to such small doses ; it is, however, almost indispensable as an adjuvant to other treatments, chiefly because of its marked effect in reducing the relapse-rate, and also because of its rapid action on the sexual, crescent forms of malignant tertian malaria, which sterilizes the patient as far as his carrier state is concerned.

Tebetren, as far as our limited experience goes, would appear to have much the same clinical effects and limitations as atebrin.

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Experience with Synthetic Drugs in the Treatment of Malaria

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The observations about to be presented relate to cases of malaria treated with synthetic drugs under a particular set of conditions. It is necessary to emphasize this because, as is well known, a treatment which appears efficacious in a certain season or locality, or for a certain class of patient, may, under other circumstances, prove disappointing.

The conditions, then, were as follows :—

Number of cases : approximately 690.

Class of patient : British officers and British other ranks.

Locality: the Punjab Province of India, except for 34 cases treated in England.
Time: 1932 to 1938.
Control and observation: all were treated by me personally or under my direct supervision.

In addition, I have included some remarks about a group of cases from the Force which operated against the Mohmands in the North-West Frontier Province in 1935.

Malaria, as seen in the Punjab, has peculiar features to be taken into account in appraising results of treatment: (*a*) the severity, of both benign and malignant tertian varieties, which are practically the only two seen, is usually mild. It was so in the period under review, except in 1933 when the number and severity of attacks was exceptional. (*b*) The season of infection is limited to about two months, that is from the end of August to the end of October, in ordinary seasons; sometimes it is rather longer and extends from mid-August to mid-November. Hence, if observations are confined to British troops, among whom reinfection while on leave is negligible, it is reasonably certain that attacks occurring in the "off season" are relapses.

The *synthetic drugs* used were (*a*) those which attack non-sexual forms of the parasite, that is to say atebrin and atebrin musonate, and (*b*) those of which the chief actions are to destroy sexual forms and relapse-producing trophozoites, namely plasmoquine and cilional (now called "certuna"). The general plan of treatment was to stop the attack with a drug of group (*a*) and then proceed with one of group (*b*).

The great majority of patients was treated with atebrin and plasmoquine, both by the mouth, in the following dosage: 0·1 grm. of atebrin three times a day for seven days, then 0·02 grm. of plasmoquine after breakfast, and 0·01 grm. after tea for five days. The patient was kept in bed during the atebrin part of the course and, all being well, was allowed up or out of hospital for the plasmoquine part.

A proportion of cases to serve as controls received quinine in substitution, or part substitution, of atebrin. In these the general plan of the atebrin-plasmoquine course already described was adhered to, 10 grains of quinine hydrochloride being considered equivalent to 0·1 grm. of atebrin. The plasmoquine part of the course remained the same throughout.

In 1932 and 1933 the plasmoquine part of the course followed immediately upon the atebrin part. During the height of the 1933 epidemic which, as already noted, was unusually severe, fever did not subside, and some patients developed abdominal colic and marked cyanosis. It was thought this might be due to administering plasmoquine while the system still contained atebrin, that is in effect, giving the two drugs together. So the urine of a series of patients was tested with ether and sulphuric acid, and it was found that it ceased to contain atebrin in appreciable quantity four days after the last dose of the drug. A four days' interval, therefore, was introduced between the atebrin and plasmoquine parts of the course. After this there was no more trouble from toxic symptoms. Later the interval was reduced to two days without ill-effect.

Response to atebrin was variable. During the height of the 1933 epidemic, when attacks were severe, the average duration of pyrexia after beginning treatment was 3·8 days; at the beginning and end of this epidemic, and in other years when the disease was milder, control of fever was obtained in about two and a half days. When an attack showed definite tertian periodicity, a common result was two paroxysms after beginning atebrin. Parasites disappeared from the blood at the same time as the pyrexia ceased.

Response to plasmoquine must be judged under two headings, namely the effect on sexual forms of the parasite, and the effect on relapse-producing trophozoites. The former is indicated by the time taken for crescents to disappear from the blood in malignant tertian cases. In three cases of which I now have notes, the average time was 3·7 days after beginning plasmoquine; in no case did they persist much longer.

The effect on trophozoites is indicated by the relapse-rate. Now, considering the features of Punjab malaria it looked, at first sight, as if this would be easy to obtain. But in the event, frequent movements of troops and medical personnel occasioned by frontier operations, reliefs, and trooping, made satisfactory follow-up of most cases impracticable. Nevertheless, some batches of benign tertian cases, amounting to 175 in all, were traced till the June following the primary attack. The relapse-rate varied considerably in individual batches, being notably higher among the 1933 cases, but there was no significant difference between atebrin-plasmoquine and quinine-plasmoquine cases. The combined average for the 175 cases was 8·6%.

Experience of atebrin musonate began in 1935. 0·3 grm. was given intramuscularly once a day for two days to a number of patients in the Mohmand Force with the object of getting them fit for evacuation as soon as possible. In this it succeeded; the men arrived at the base in excellent condition and were then given a course of plasmoquine. At the same time the drug was employed for a few local cases with severe symptoms or in which vomiting made oral administration unsatisfactory. In these cases it never failed to cut short an attack within two days. It was not tried in cerebral cases.

43 men of the Mohmand Force who had received atebrine musonate as described above were kept under observation in a non-malarious hill station by Captain E. H. P. Lassen, R.A.M.C., until the following September. Among them the relapse-rate was 37·2%.

Thereafter the two days of atebrin musonate by injection was supplemented by five days' atebrin by the mouth.

Cilional (certuna) was used in 61 cases in place of plasmoquine. The dosage was 0·02 grm. three times a day for five days in benign tertian and seven days in malignant tertian concurrently with atebrin. 24 of the men almost immediately went to the Frontier and were unget-at-able. Of the remaining 37, eight had relapsed by December 31; this is a relapse-rate of 21·6% in two months.

Toxic phenomena were occasionally encountered.

When, as previously noted, atebrin and plasmoquine were in the system together because sufficient time had not been allowed for the former drug to be excreted, a proportion of patients (about 25%) was affected by abdominal colic, marked cyanosis and, rarely, vomiting. All of them recovered quickly on stopping the drugs.

During the atebrin part of the oral course a few individuals had mild transient abdominal colic, not bad enough to interrupt treatment. One patient in England developed a state of acute anxiety and self-abasement. He was of psychoneurotic type and recently had undergone considerable emotional strain. He recovered in four days.

In one case of malignant tertian malaria admitted with hæmaturia and treated with atebrin musonate the systolic blood-pressure fell to 50 mm. of mercury with anuria for two days. This may have been due to atebrin or to hæmorrhage into the suprarenals as well as into the kidneys. Recovery was rapid. Otherwise no toxic effects of atebrin or atebrin musonate were observed.

Plasmoquine, when separated from atebrin, appeared to be responsible for a few cases of mild abdominal colic and cyanosis, but never caused symptoms severe enough to interrupt treatment.

Cilional gave rise to no unpleasant effects.

To summarize and comment:—

(1) In controlling the attack there was little to choose between oral atebrin and oral quinine given as described above; quinine possibly reduced the fever more quickly, while atebrin caused no buzzing in the ears, upset the digestion less, and was preferred by patients; they looked, and said they felt, better even while still running a temperature.

(2) Atebrin musonate intramuscularly, in a small number of cases, seemed as effective as intravenous quinine, and was more convenient to administer. It was not tried in cerebral malaria.

(3) Plasmoquine appeared to be remarkably potent in clearing the blood of crescent forms of *Plasmodium falciparum*.

(4) The effect of plasmoquine on relapse-producing trophozoites is indicated by a relapse-rate of 8·6% among 175 benign tertian cases under observation in 1932, 1933, and 1934, which had been treated with various combinations of atebrin, quinine, and plasmoquine, and followed up till the next June. It is to be noted that this period of observation catches the "spring relapses" which are a feature of Punjab malaria, and in many years probably includes the bulk of relapses. Later experience, especially in 1936, showed that a batch of relapses sometimes occurs in late July and August. These would make the average rate over a longer period of years higher.

The series, however, *is* valid for comparison with a series of over 100 Punjab cases treated with long courses of quinine and followed up till June by me personally in 1924 and 1925. The relapse-rate for this latter series was over 25%.

Since there was no appreciable difference in the relapse-rates of atebrin-plasmoquine and quinine-plasmoquine cases, it is to be presumed that the benefit was due to plasmoquine.

(6) The number of cilional cases was too small to allow of conclusions being drawn.

(7) Provided precautions were taken the possibility of toxic effects did not cause undue anxiety.

Discussion.—Lieutenant-Colonel J. S. K. Boyd drew attention to certain figures compiled from the Monthly Returns of hospitals in India. It might be accepted as a general rule that, while cases of malaria occurring in India in the July to December period were both fresh infections and relapses, the vast majority of cases occurring from January to June were relapses only. When plasmoquine was introduced, there was a fall in the total number of cases of malaria, and an analysis of the monthly incidence, January to June period, showed a decline which was relatively much greater than that in the June to December period. This was obviously due to the reduction of relapses, and substantiated the claim that plasmoquine—given of course in addition to quinine or atebrin—possessed the property of bringing this about.

Apart from statistics, which were apt to be regarded with suspicion, there was one incontrovertible argument in favour of plasmoquine treatment.

Colonel Smith had mentioned the Malaria Treatment Centre at Kasauli. From his point of view it was a centre where the treatment of malaria could be scientifically studied. From the point of view of the harassed medical officer in a malarious station in the plains it was a haven to which he could dispatch those depressing cases of recurrently relapsing malaria which resisted all treatment. In the pre-plasmoquine days there was a waiting list of such cases in most hospitals from which selections were made as vacancies occurred in Kasauli, which was normally full to capacity. In 1931, when plasmoquine was used on a large experimental scale in the most malarious stations, the Centre admitted every applicant and was only half filled. In 1932 and 1933, despite repeated reminders to hospitals, the numbers fell to a quarter of its capacity, and even so, the cases were not the chronic relapsing type previously admitted. In March 1934 the Malaria Treatment Centre was closed for want of material. There could be no reasonable doubt that this happy state of affairs was attributable to plasmoquine treatment.

Colonel A. D. Stiring: Before the advent of the newer antimalarial drugs I found that, at Calcutta, the regiments arriving there heavily infected with malaria from up-country gradually became more or less free from malaria after the first year. Thus, one regiment had 105 cases in 1921, 37 cases in 1922; and another had 90 cases in 1923; 23 cases in 1924. These regiments were located in Fort William under strict military control. Places where mosquito larvæ were found breeding were notified in District Orders, and treated, with the result that such cases as did occur in the second year were for the most part found to have been contracted either on duty or leave outside Calcutta.

Air Commodore H. E. Whittingham said that the low relapse rates of cases of malaria treated by atebrin and plasmoquine, quoted by Colonels Smith, Lipscomb and Boyd, are only true up to a period of about three months after commencing treatment. Following up cases of malaria in the R.A.F. which had been treated with atebrin and plasmoquine courses, it was found that 20 to 25% relapsed, which closely approximates to the 23% relapse-rate recorded for the U.S.A. Army in the Panama Canal zone when treated with atebrin and plasmoquine, if watched over a period of three

years, but it is agreed that these new synthetic drugs have a marked effect in reducing the relapse-rate. Thus, for all cases treated with quinine, the relapse-rate is approximately 40%, with plasmoquine about 10%, and with atebrin about 5% over a three-months' period. In treating any case of malaria we must clearly keep in mind the pathological process underlying the infection.

(*a*) Malaria parasites very rapidly take to cover in the internal organs in close relation to the reticulo-endothelium. This process takes place so quickly that it has not been found possible to transmit malaria by blood collected from persons inoculated with malaria an hour or so previously. Many of the parasites are lodged in the splenic sinuses, where they tend to escape the free circulation of blood, including blood containing various medicaments which are intended to kill off the parasite. For this reason it is important in treatment to drive the parasite out into the blood-stream by some provocative agent such as adrenaline or novarsenobillon (apparently from Colonel Smith's observations atebrin acts in a similar manner).

(*b*) The next point to visualize is that a malarial parasite is most vulnerable when it is free in the blood-stream, that is during the actual pyrexial period when, unfortunately, antimalarial drugs cannot be given by the mouth, as they cannot then be absorbed owing to alimentary congestion ; in fact they are liable to be vomited. Intravenous medication is the best means of killing off parasites during the pyrexial period, but the dose must be so regulated that it does not cause too great a reaction in the process.

(*c*) The malaria therapy of general paralysis of the insane has shown that there is a definite process of immunity to malaria, as certain cases that have been treated with one type of parasite cannot be reinfected with that species. To help develop immunity to malaria it is necessary to regulate the dosage of drugs so as to weaken or kill off the malaria parasite without injuring the tissues of man, as damaged or devitalized tissues form a nidus for the parasites and aid them in their struggle for existence.

(*d*) It is only necessary to treat malaria relapses. During the Great War we had glaring examples of the damage done to the individual by over-treatment with quinine. It is wise to ascertain the relapse period of each case of recurrent malaria and give the appropriate medication just prior to the expected relapse so as to keep the disease in check and allow the body to develop its own immunity.

(*e*) Metabolism must be regulated as regards acidosis and hypoglycæmia which occur during acute malarial attacks, as pointed out by Sinton many years ago. For this reason alkalis should be freely administered, and they have the further beneficial action of rendering alkaline and soluble any blood pigment that is being excreted ; whereas otherwise it would be in an acid and insoluble form and tend to block the tubules of the kidneys as is known to occur in blackwater fever, which, I think we may assume, is a complication of malaria. Glucose should be given freely to counteract the hypoglycæmia, and this has the further value of protecting the liver from damage by such drugs as plasmoquine, atebrin, and the arsenicals.

(*f*) There are certain precautions to be taken in the administration of atebrin : it is not advisable to give it to those who are known to be alcoholics. Acute jaundice developed in two such cases under my care, and the case of death reported by Colonel Smith would appear to be another such. Those having atebrin treatment should be warned not to expose themselves to direct sunlight more than possible for three or four weeks after treatment, as cases occur when sun-bathing has been indulged in where pigmentation is fixed in the skin for some considerable time.

(*g*) Novarsenobillon as a form of treatment for malaria is not generally appreciated. I read a paper on this subject before this Section as long ago as 1925 (*Proceedings* **18**, War Section, 23). This drug not only tends to drive the parasites into the circulation but is also lethal to them and is a good general tonic. Its use is not recommended in primary attacks of malaria but more for recurrent ones, and the procedure to be recommended is as follows :—

0·45 grm. of novarsenobillon is given in the morning to drive parasites into the circulation and to damage a certain number, then 10 gr. of fluid quinine are given at night time and 10 gr. three times the following day to complete the action against the parasites. Further injections and quinine treatment are given at weekly or fortnightly periods, depending on the relapse period, until six or eight treatments have been given. If this treatment is given at the week-end the patient is usually fit for duty during the working week.

Section of Otology

President—E. D. D. Davis, F.R.C.S.

[*March* 3, 1939]

DISCUSSION ON MALIGNANT DISEASE OF THE EAR (EXCLUDING THE PINNA)

Mr. Philip Scott: This paper is an analysis of 70 cases of malignant disease of the ear, of which 12 have not been previously published. I shall describe five cases which I have seen during life, in greater detail; two of these patients are still living (Cases 3 and 17), and I shall show lantern slides prepared from serial sections of the temporal bone of one of the fatal cases (Case 1).

Malignant disease of the ear, excluding the pinna, has been accounted a rare disease.

Sir William Macewen, writing in 1893, recalled only three cases of carcinoma of the middle ear.

Bezold, in his textbook of Otology (1907) said that in his own statistics he could count only three examples of sarcoma and one of carcinoma of the middle ear, i.e. one case of malignant disease of the ear in every 5,000 ear patients.

Edward Dench of New York, writing in 1895, stated that only two cases of malignant disease involving the meatus came under his observation.

In June 1930 the late J. S. Fraser quoted the statistical tables of the Ear Department of the Royal Infirmary, Edinburgh, with Logan Turner. There were 13 cases of malignant disease out of 6,605 patients with the external meatus affected by disease, i.e. 0·197%.

After reading these authorities, one might expect to find a scarcity of reported cases, but in actual fact there are plentiful records, and I have read the reports of 70 cases, the majority of which have been published in the *Proceedings* of the Section of Otology of the Royal Society of Medicine during the last thirty-one years.

It is obviously unwise to draw any conclusions from these figures, but it would seem that either malignant disease of the ear is becoming less rare or that, owing to greater facilities for examination, fewer cases pass undiagnosed.

This suggestion is not purely of academic interest, because until late in the course of the disease the symptoms are not pathognomonic, but are those which occur in commoner ear conditions, namely otorrhœa, with or without bleeding, deafness, pain, and vertigo; facial paralysis and visible swelling or ulceration being as a rule signs of advanced disease.

In order to make this early diagnosis in a disease which so often presents itself in disguise, it is essential to consider the symptoms and signs to which it may give rise,

and in what way they may be distinguished from those of the disease it simulates.

Careful analysis of the records of the 70 cases shows that only 19 patients presented themselves with symptoms which immediately aroused suspicions of malignant disease. Of the remaining 51, the majority had otorrhœa, with blood-stained discharge in a few cases ; 19 had chronic suppurative otitis media, with or without vertigo and pain ; 8 furunculosis or meatal eczema ; 15 patients had facial palsy when first examined by an otologist. Many had some degree of deafness. One patient, complaining of pain, was treated for one year for wax before seeing an otologist who removed the " wax " scab and revealed an ulcer in the external meatus (Case 48).

These facts show that very few of the patients complain of the discharge, many having become accustomed to it, and that the onset of pain or irritation, with or without vertigo or deafness, brings the majority to the aural surgeon for the first time.

Among the factors which may arouse suspicion of malignancy are :—

(1) Toughness of granulations when touched with a probe.
(2) Recurrence after removal and a tendency to bleed easily.
(3) Persistence of meatal infection in spite of cleansing treatment.
(4) Pain on chewing. This point was stressed by Dr. Albert Gray.
(5) The presence of granulations or papillomata attached to the deep meatal wall.

Examination of the meatus in these cases may be difficult, and sometimes it is only after all sodden epithelium or wax has been carefully removed that an ulcer in the deep meatal floor becomes visible. In every case the diagnosis must depend upon the histological examination of tissue removed.

Pathology.—Malignant disease of the ear is divided into four groups.

(1) Carcinoma.
(2) Sarcoma.
(3) Rodent ulcer.
(4) Endothelioma.

Whilst examining the microscopic slides from several of the cases recorded in the appendix, it occurred to me that it might be helpful to know to which of Broder's groups each belonged. I thought it might enable one to decide in a doubtful case whether a " sleeve resection " operation on the meatus was sufficient or whether the radical excision with diathermy was necessary. Dr. H. F. Brewer examined the slides from 14 cases and found that the groups were apportioned as follows :—

Group 1	4 cases
Group 2	5 cases
Group 3	2 cases
Rodent ulcer	3 cases

It is difficult to draw any definite conclusion from so few instances, but in Group 1 two patients died with rapid recurrence after a very radical operation, and two cases are still alive after the radical operation, one twenty-two years (Case 29) and the other fifteen years (Case 42) later.

In Group 2 one patient is still alive fourteen years later (Case 43), two died from recurrence within two years of operation, and two cannot be traced. In Group 3 one patient survived for nine years, but died with recurrence (Case 28), and one (Case 63) surviving eight years. Of the three cases of rodent ulcer, two cannot now be traced, and the third, reported as squamous-cell carcinoma in 1917 (Case 64), died in 1921 with extensive erosion of the skull.

Carcinoma.—By far the commonest type of malignant disease to affect the ear, may be primary or secondary.

A few cases of secondary deposit of carcinoma in the temporal bone from primary

growths in the breast (Case 40), the prostate and kidney (Case 19) are on record, and at least one case in which the ear was invaded by direct spread from secondary cervical glands (Case 36).

Primary carcinoma, almost always squamous-cell type, but sometimes an adenocarcinoma, may be divided into two main groups, identified by early or late involvement of the tympanum. Some growths have been recorded as arising within the middle-ear cavity, but Mr. Ernest West believed that all squamous carcinomata arose somewhere in the fundus of the external meatus, and spread inwards to involve the tympanum early. The meatus appears to be the starting point in the majority of instances.

In the second group the tympanum is not involved until late in the disease ; it is the primary ulceration in the meatus which usually attracts the patient's attention by giving rise to pain or irritation and discharge before the growth has spread widely. In some cases it is not possible to decide from which part the growth arose.

The distinction between these two groups may be of considerable moment, for if the meatus alone be affected it may be possible in some instances to avoid opening the mastoid and disturbing the drum and ossicles. On the other hand, if there be the slightest suspicion of involvement of the drum membrane or tympanum, or if facial paralysis be present, a radical mastoid operation will be necessary in addition to excision of the meatus.

In the first group the symptoms are those of chronic suppurative otitis media, which in fact has usually preceded the more serious disease by many years. Differentiation should be made before facial palsy is present, or the growth will almost certainly be inoperable. All cases in which granulations are present, especially if the patient be over 40, require close observation, and if these granulations are tough or tender and show a tendency to bleeding or recurrence after removal, the possibility of malignant disease should be considered. Since this disease is relatively rare as compared with chronic otitis media and cholesteatoma, the decision to explore the mastoid may be made on the grounds of the commoner condition, but it would be wise for the surgeon to bear the possibility of malignant disease in mind in all cases presenting any unusual features.

In the second group in which the meatus is first involved, the symptoms are more commonly those of a severe otitis externa, pain, irritation, and discharge. The diagnosis will depend upon thorough examination of the meatus, not necessarily at the first visit, when the meatus may be too swollen and tender, but after a short course of cleansing treatment, when the concurrent infection has subsided. Granulation, ulceration, or papilloma, especially on the floor or anterior meatal wall, should justify examination under anæsthesia and biopsy.

Of the other types of malignant disease, sarcoma and endothelioma present few features which, apart from histology, serve to distinguish them from carcinoma.

Contrary to the usual age-incidence, and to the accounts by early writers, sarcoma, of which there were four examples in this series, arose within the third, fourth, and fifth decades and not in childhood. The only specific reference to a case of growth occurring in a child, proved on section to be a case of endothelioma, which was reported by Sir James Dundas-Grant in 1910. The boy, aged 6 years, had had three previous operations, and there was swelling and multiple fistulæ over the mastoid. Sarcoma was suspected but section proved it to be a typical endothelioma (Case 18).

There were six other cases of endothelioma, one of which had unusual features, to which I shall refer later.

The characteristics of rodent ulcer need no special comment, but its slower rate of growth and the persistence with which it recurs with a tendency toward increased malignancy leads me to think that diathermy excision, as for a Broder's Group 1 carcinoma, offers the best chance of a permanent cure.

Treatment

Treatment by surgical measures may be divided into two essential groups: (1) Meatal operation. (2) Radical.

(1) *Meatal.*—When there is an ulcer in the meatus without any apparent involvement of the tympanic membrane or past history of chronic suppurative otitis media, sleeve resection of the meatus, with the skin of the bony meatus, and in some cases the pinna, has been carried out with some measure of success, especially if followed by some form of radiotherapy. Diathermy knife is to be preferred to cold scalpel.

(2) *Radical.*—When there is the slightest doubt about the integrity of the drum membrane, or if chronic otitis media has preceded the onset of malignant disease, radical mastoid operation, together with the meatal excision should be performed. Subsequent use of diathermy or radiotherapy has been recommended by several writers, and is in accordance with present-day methods of treating malignant disease of other organs.

Of the 70 cases noted in the appendix, the form of treatment is recorded in 60 cases. Of these,

Complete surgical excision alone was carried out	in	26 cases
Complete surgical excision combined with diathermy	in	10 cases
Complete surgical excision combined with radiotherapy	in	14 cases
Radiotherapy alone	in	10 cases
Operation refused or treatment not recorded	in	10 cases

Unfortunately in very few of these cases are there records of progress apart from those cases recorded as having died. This may have led to an unnecessarily despondent view of this form of malignant disease in which lymphatic spread is often late and the rate of growth slow, and in which, therefore, if excision of the primary growth be radical enough, the prognosis should be less unfavourable.

Two of the following five cases, while appearing to decry this relatively optimistic view, nevertheless serve to show the extremely slow rate of growth in some cases, and incidentally point to the necessity for frequent "follow-up" examinations.

Case 1.—No. 189R. *Epithelioma involving the middle ear.*

W. D., male, aged 64.

History.—1894: Forty-two years ago when aged 22, first noticed a pimple on the right pinna, which became ulcerated. This improved with some radiation treatment.

1912: Received X-ray treatment.

July 1914: Diathermy excision of an ulcer on the upper part of the pinna.

December 1914: Mr. West excised the cervical glands by block dissection.

He remained well from December 1914 until April 1936, a period of twenty-one and a half years. He then noticed some discharge from the right meatus, and was rather deaf.

October 1936: The fundus of the right external auditory meatus was filled with friable growth, but the site of the original ulcer on the pinna was sound. There were no enlarged glands to be felt in the neck. There was a small rounded pimple on the face, 1 in. lateral to the outer canthus of the right eye. There was slight facial weakness.

The meatal floor was split with a diathermy knife, and the growth from this region was removed. There were no recognizable landmarks, but the mastoid region and tympanum were not explored. The pimple was excised with diathermy.

Section of tissue from ear and face showed squamous-cell carcinoma.

He died two months later of bronchopneumonia following an accident, and at the autopsy macroscopic examination of the right petrous bone revealed that growth had eroded the body of the bone, and was projecting on the posterior surface of the bone just behind the internal auditory meatus, where there was local meningitis.

The temporal bone has been prepared by decalcification and embedding in celloidin at the Ferens Institute of the Middlesex Hospital, and photomicrographs of sections are shown in figs. 1–6

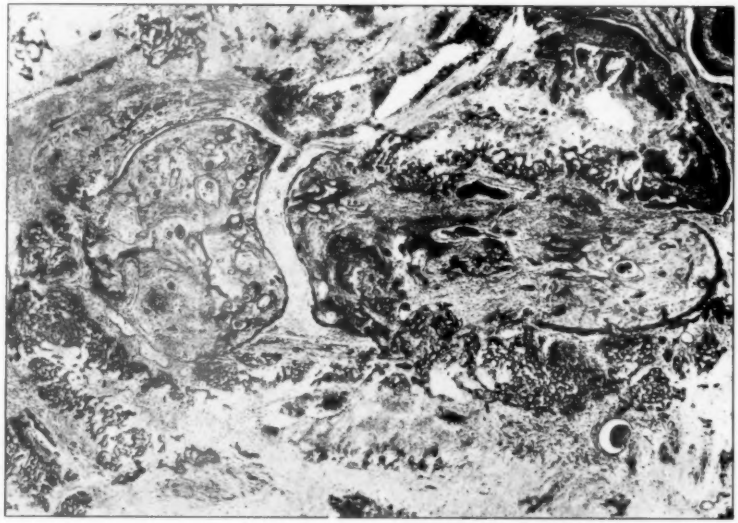

FIG. 1.—No. 189 220. The joint between malleus and incus. This shows involvement of the incus by growth, with maintenance of the normal outline.

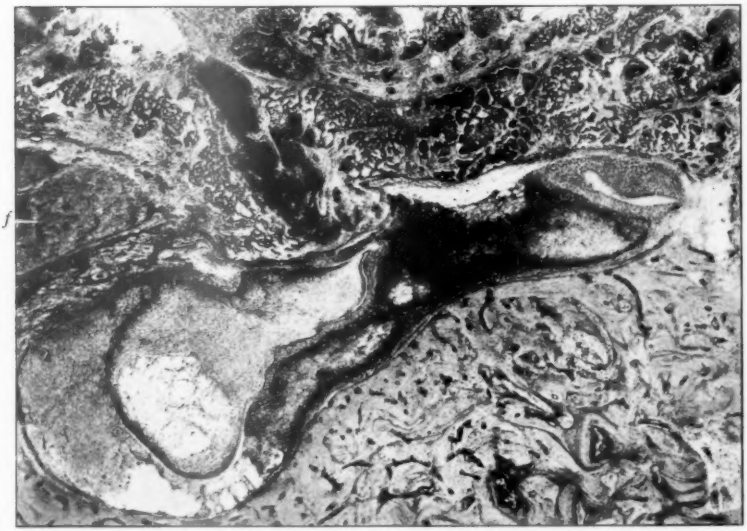

FIG. 2.—No. 189 250. The section passing through the horizontal canal. There is no growth within the endosteal space, which has been compressed in one part; the facial nerve (*f*) can be seen in the top left hand corner of the slide, and there are a few malignant cells between its fibrous sheath and the vestibular cavity.

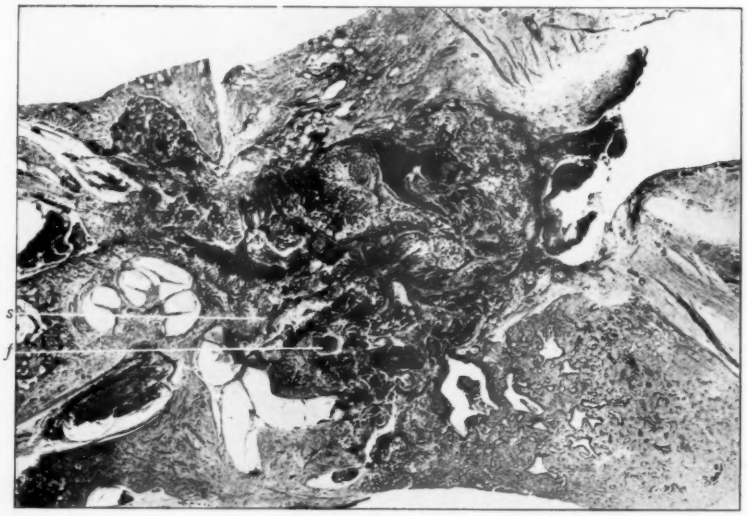

FIG. 3.—No. 189/340. Section through the modiolus of the cochlea, and through the foramen ovale. Note absence of the stapes footplate from the oval window. The stapes, *s*, is lying free in the middle ear cavity, surrounded by growth. Behind and a little external to it the facial nerve, *f*, can be seen lying completely innocent of any bony canal, but surrounded by a thick fibrous sheath. There is no invasion of the nerve, but it is interesting to recall that this patient had only slight facial paralysis.

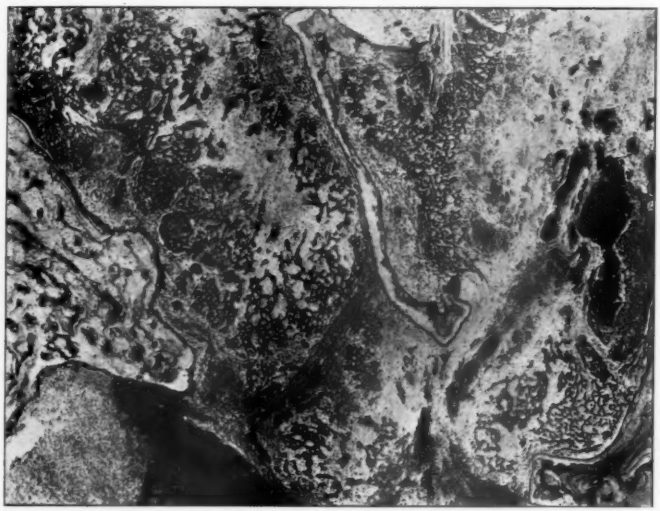

FIG. 4 A.—Stapes footplate dislocated.

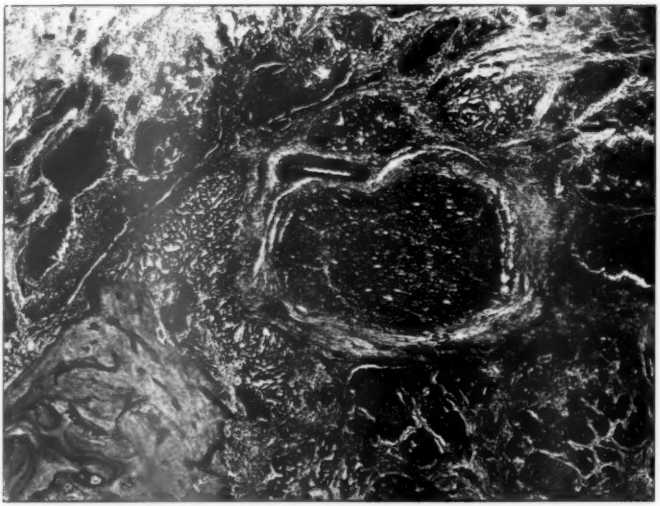

FIG. 4 B.—Facial nerve surrounded by growth.

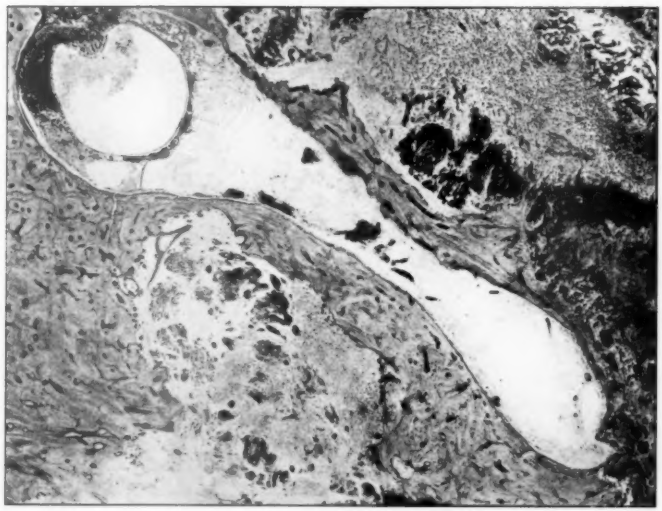

FIG. 4 C.—Posterior canal surrounded by growth.

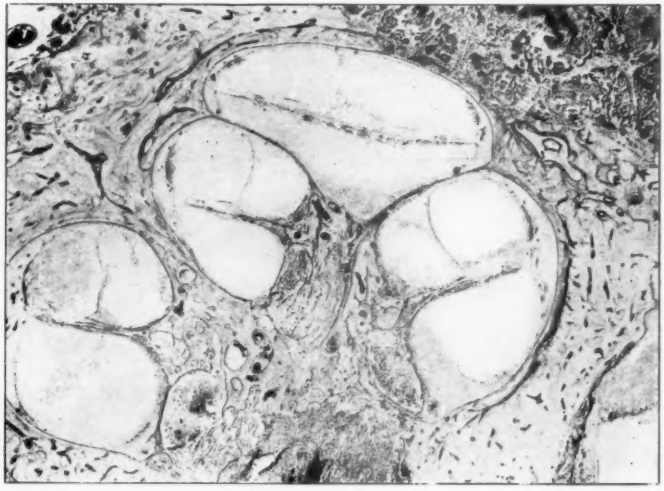

FIG. 5 A.—Whole cochlea. There is suppurative labyrinthitis, with pus cells in the scalæ, and considerable increase of endolymphatic pressure. There is also erosion of part of the labyrinthine capsule near the apical whorl.

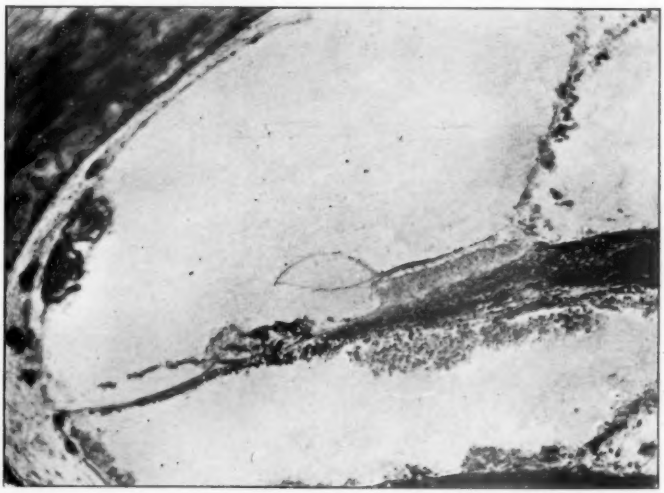

FIG. 5 B.—Scala media, showing distension, with displacement of Reissner's membrane. Pus cells in scala tympani.

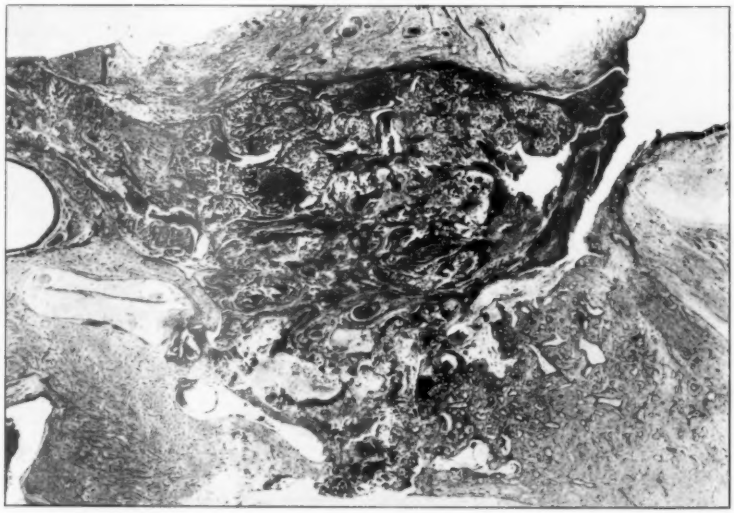

FIG. 6.—Section through round window and posterior semicircular canal.

Case 2.—? Adenocarcinoma involving the middle ear.

G. H., male, aged 62.

History.—1918, when aged 45, first noticed a small hard pimple on the right side of the face between the eyebrow and the pinna.

February 1922: This commenced to break down in the centre, and he noticed a watery discharge.

May 1923: There was a circular plaque 1½ in. in diameter in the skin, ulcerated in the centre, and covered with a scab. It was adherent to the underlying structures. Clinical diagnosis: Rodent ulcer.

Operation.—Excision of the ulcer with surrounding skin, 2½ in. by 2 in.

Section: Chronic inflammatory.

1932: He noticed a small ulcer on the right side of his face, in front of his ear. Later he had pain in the right eye, and a corneal ulcer was found and carbolized.

1933: He was readmitted with an indurated ulcer in front of the right ear. The right upper and lower eyelids were swollen, and there was a swelling at the outer canthus of the right eye. His sight was very poor.

Operation (Mr. Harold Wilson).—Excision of the right eyeball and lids with the deep fascia, and periosteum. The ulcer in front of the right ear was irradiated with 9 mgm. radium (interstitial) for seven days.

Section: Basal-cell carcinoma, in parts almost epitheliomatous.

January 1936: Seen in the aural department at St. Bartholomew's Hospital for the first time. He complained of deafness and discharge from the right ear for twelve months; no pain.

The right eye socket was covered entirely with smooth skin. There was a smooth healthy scar on the face at the site of the previous ulceration. There was no visible ulceration on the face, but there was a scarcely perceptible filling out of the right temporal fossa. Movement of the right temporomandibular joint free.

Ears: Right ear. Hearing extremely poor, deafness of doubtful type. Labyrinth reactions not recorded. No vertigo. There was an ulcer visible in the deep meatus on the anterior wall. The tympanic membrane was not visible.

Operation (Mr. Sydney Scott).—Diathermy cutting. January 1936. Curved incision above the pinna. The pinna and meatus turned downwards. The bone of the squama, under the zygomatic

arch, was found to be eroded by growth, exposing the dura mater of the middle fossa. The growth extended forwards and medially along the base of the skull, outside the cranium along the line of the external pterygoid muscle. The zygomatic arch was partially deficient, and growth had spread into the temporomandibular joint, which was completely disorganized. The mastoid was opened with a gouge, and dura mater of the middle fossa exposed until a normal area around plaques of growth was visible. Diathermy button applied to these plaques. It was then found that the growth had extended too far forwards towards the sphenomaxillary fossa to be entirely removed. The pinna was loosely sutured in position and the wound packed.

Three weeks later he suddenly developed erysipelas and pyæmia, and he died February 18, 1936.

Section : " No involvement of growth in the ossicles. The tumour has characteristics intermediate between those of rodent ulcer with cystic change, and a sebaceous adenoma, and should be regarded as malignant."

Post mortem : Extensive growth extracranial, along the base of the skull. Growth adherent to the dura mater, as seen at operation, but no intracranial metastasis. No meningitis.

Case 3.—*Squamous carcinoma of the external meatus.* (Published in *Proc. Roy. Soc. Med.*, **28**, 1108. Sect. Otol., 63.)

J. M., male, aged 36.

History.—Lupus vulgaris on the face for many years. Repeatedly treated with ultra-violet light.

January 1932 : Epitheliomatous change suspected. An ulcerated area on the right side of the face anterior to the tragus. $3\frac{3}{4}$ in. by $1\frac{3}{4}$ in.

Operation.—Radium needles inserted around and under the ulcer. Biopsy report doubtful.

July 1932 : Severe pain radiating down the jaw and around the periphery of the pinna, and up to the temporal region. There was an obvious recurrence in the external meatus 1 in. by $\frac{3}{4}$ in. Diathermy excision of the pinna and cartilaginous meatus including the skin of the bony meatus, dividing some of the fibres of the facial nerve. The bone was not opened as the drum membrane was not involved.

Section : Well-differentiated squamous-celled carcinoma.

The wound healed by granulation and epithelialized so completely to the edges of the bony meatus that no skin graft was necessary.

This patient is still under treatment for lupoid condition of the skin elsewhere in the body, but there is no evidence of recurrence of malignant disease six and three-quarter years after his last operation.

Tympanic membrane intact. Hearing good.

Case 4.—Mrs. E. J. H., female, aged 64.

History.—First seen September 1931, by late Mr. Just, at St. Bartholomew's Hospital.

November 1930 : Shooting pain around the pinna, which was very tender at this time. Pain continued on and off until after Christmas 1930, when there was watery discharge from the meatus, which was thought to be eczema, and was treated with drops.

Easter 1931 : Abscess appeared behind the left ear, which was lanced. The wound healed in about ten days, but almost at once another swelling appeared and was again lanced. Since that time the wound never healed, there was no pus, but free bleeding at the second operation.

Pain persisted and was shooting in character, over the head, neck, and face. There was slight deafness.

September 1931 : No discharge from the meatus, but a hard lump appeared at the apex of the mastoid. There was no facial palsy.

On examination (Mr. Just).—The meatus was almost completely blocked up by bulging of the floor and posterior wall ; no ulceration or bleeding. The lumen was too narrow to allow the drum membrane to be seen. Behind the pinna there was a large curved ulcer with everted edges, and an irregular base covered with slough, bleeding readily on touch, and very painful. The pre-auricular glands were enlarged and adherent to the skin. There was no facial paralysis, nystagmus, or giddiness. Jaw movements were complete and painless, but slight stiffness.

Treatment.—The growth was considered too extensive for radical operation, but deep X-ray treatment was given to relieve pain. She died in May 1932.

Case 17.—*Hæmangio-endothelioma of external meatus.*

Mrs. S., female, aged 62.

History.—Deaf in both ears progressive for thirty years. ? otosclerosis.

1934 : Granulations in the deep meatus, left ear. No discharge. Treated several times during the next three years with chromic acid. Refused any operation.

December 1937 : Again examined in out-patients. There was a firm pulsatile, bright red swelling attached to the floor of the meatus. Apart from the pulsation, which was not easy to discern, this had the appearance of a simple aural polypus, but there was no otorrhœa, and careful probing revealed that it arose from the floor of the meatus. There was no ulceration.

May 1928 : She finally agreed to have an operation, and the polypoid swelling was removed with a snare (Mr. Sydney Scott). There was profuse hæmorrhage, controlled by packing in the meatus.

Biopsy : The specimen consists of a small brown tumour. Section shows it to consist of a mass of somewhat rapidly growing vaso-formative tissue in which there are irregular spaces containing blood. Conclusion : Hæmangio-endothelioma.

Operation.—Diathermy excision of the posterior meatal wall, including the base of the polypus, through a post-aural incision.

February 1939 : There is a smooth epithelialized cavity in the meatus ; there is no recognizable drum membrane, but an adventitious membrane distends on inflation with a Eustachian catheter. There is no evidence of recurrence.

In conclusion.—I am indebted to all those members who have taken the pains to record cases in the *Proceedings* of the Society, and in particular to Mr. Sydney Scott and the late Mr. Just, for giving me the opportunity of seeing their cases at St. Bartholomew's Hospital, and for permission to refer to the case notes.

I should like to thank Dr. H. F. Brewer for taking so much trouble in classifying many of the sections.

The serial sections were prepared at the Ferens Institute of the Middlesex Hospital. I am indebted to Mr. Cleminson, the Honorary Director for many facilities, and to the technical staff, in particular Mr. Pilgrim, for assistance in this connexion.

This paper is part of the work in which I am engaged as Geoffrey Duveen Student of the London University.

Mr. Lionel Colledge : *Carcinoma of the middle ear.*—I will try to present a composite account of the clinical and pathological features of carcinoma of the middle ear, derived from my own experience and from some points mentioned in the literature. That it is quite uncommon if not actually very rare is shown by the following circumstance. I inquired from a friend who has for many years been Superintendent of one of the large County Council hospitals near London, if he could tell me of any cases. He could not recall one case, and could only say that if there had been any the disease had gone unrecognized. It is most unlikely that this could happen in the later and terminal stages, however difficult the early diagnosis may be.

In defining malignant disease in this situation it is necessary to include the petrous portion of the temporal bone and the deeper portion of the external auditory meatus, but disease of the pinna itself is expressly excluded.

In discussing the ætiology most writers lay great stress on a long history of chronic otorrhœa preceding the development of the tumour. This is usually so, but not always, and Berendes has recorded the case of a woman aged 39 in whose middle ear a squamous epithelioma arose without any previous suppuration. Therefore while old disease of the middle ear must be conceded as an important ætiological factor, it is not an essential one. In the matter of age the incidence of malignant disease here seems to be much the same as in other situations, essentially an affection of the middle aged, but I have seen sarcoma of the middle ear in a boy, and epithelioma of the middle ear in an old lady of 93.

It is natural to regard malignant disease in the temporal bone as a primary manifestation and rare at that, but it may arise even more rarely as a secondary deposit from a carcinoma in some common situation such as the breast, and Přecechtel mentions the case of a sarcoma arising in the right middle ear eighteen months after excision of the left eye for an intra-ocular sarcoma.

The most common type of tumour arising in this situation is the squamous-celled epithelioma with keratinization, though this does not seem to conform with the histological character of the epithelium lining the middle ear. Possibly such tumours arise in the deep part of the external meatus in the neighbourhood of the tympanic ring. In addition to epithelioma, I have encountered two cases of tumours of the salivary gland class, and also as mentioned already sarcoma. Hæmangioma and hæmangio-endothelioma have also been reported.

The clinical course of malignant disease in the temporal bone seems to be dominated by one rather curious factor which is observed also in tumours arising in other parts of the skull. The dura mater offers a strong resistance to penetration by the tumour which spreads relatively easily through the bone. There may be therefore an enormous destruction of bone before a fatal issue ensues from some intracranial complication.

The effect of this mode of spread is illustrated by the case of a woman aged 42, whom I was able to keep under observation from the time I first saw her until she died, though no autopsy was available.

She had been treated for six months for boils and otitis externa, but this condition was really a carcinomatous infiltration of the deeper portion of the meatus. She suffered intense and continuous pain. When the ear was turned forward and the mastoid process laid open the dura mater of the middle fossa was found to be covered with growth giving the appearance of a coat of sugar icing. This patient obtained some relief from the operation but later suffered from severe trigeminal neuralgia, without doubt caused by a spread of growth over the dura mater until the gasserian ganglion was reached. This happened before any sign showed of the terminal intracranial extension.

In connexion with the case two other instructive points may be mentioned. A facial palsy developed, as might be expected, but quite late in the course of the disease, and secondly, an attempt was made to treat the growth with radium after exposure by operation. The application of radium needles caused violent stimulation of the labyrinth. The vertigo, nystagmus, and vomiting so produced were intolerable, and this line of treatment had to be abandoned.

The clinical course is also illustrated by the case of a man aged 42 who was admitted to St. George's Hospital eight years ago for an abscess in the right side of the neck. He was found also to have a purulent discharge from the ear and the meatus was filled by a polyp. The abscess was drained, but he declined further treatment. Seven months later a radical operation was performed on the right ear. The granulation tissue in the cavity was of a peculiar and unusual texture, and was therefore preserved for microscopic examination. A very wide radical operation was done and the post-aural wound left open. The tissue removed proved to be endotheliomatous, that is belonging to the salivary gland type of tumour, but complete healing took place and the man remained well for more than two years, when a recurrence took place in the cavity. He was given deep X-ray therapy at St. Thomas's Hospital. This caused the growth to shrink remarkably, but it did not disappear; radionecrosis followed, and the patient succumbed to a complication in the posterior fossa.

In the matter of diagnosis the comparative rarity of the disease is likely to cause it to be overlooked at an early stage unless the possibility is kept in mind. As it generally supervenes on chronic suppuration in the middle ear the onset is likely to be masked by the suppuration, but granulation tissue without suppuration or spontaneous bleeding from the ear may arouse suspicion, so that early diagnosis can be made by biopsy.

A man aged 44 underwent laryngectomy for a cancer of the larynx in 1921. Five years later he came to report himself, but asked also that his right ear should be examined because it felt heavy and uncomfortable. A red granulation was seen pouting through the tympanic membrane. Biopsy showed a squamous-celled carcinoma. This may conceivably have been an isolated secondary deposit, but it is far more likely to have been another primary growth. There was no evidence of suppuration nor inflammatory change in the middle ear. This patient was subjected to the very radical operative treatment, which I shall describe shortly, and remained well for ten years.

In the later stages of the disease facial paralysis associated with sanious discharge and infiltration of the integuments both in front and behind the pinna, besides the meatus itself, make the diagnosis obvious.

Albert Gray called attention to pain on chewing as an important diagnostic symptom, but this indicates infiltration in the neighbourhood of the temporomandibular joint and it can therefore hardly be regarded as an early symptom. The same applies to the characteristic symptoms of facial palsy, persistent hæmorrhage, and severe pain.

Deep infiltration of the petrous portion of the temporal may produce also the syndrome of the jugular foramen with paralysis of the palate, tongue, vocal cord, and sternomastoid. I have had under observation one patient in whom all the cranial nerves from the 7th to the 12th included were involved on the right side.

The prognosis is naturally extremely grave, as early diagnosis must be rather exceptional, the tumour is not very amenable to excision in view of its situation, and being surrounded by bone is unfavourably placed for radiation. In such circumstances it is natural to inquire what benefit can be obtained by radiation. It may not be tolerated at all, and it is likely, if not certain, to produce a radionecrosis of the skull. The most that can be expected is that it will cause the growth to shrink for a time, and it may be employed as a temporary palliative.

Provided the growth has not advanced to the stage of diffuse infiltration and is still in a reasonably early stage, the best treatment is excision. As the growth tends to spread outwards and invade the external auditory meatus, the excision should include the pinna with the surrounding skin and the meatus. The pinna is surrounded by an elliptical incision, the superficial temporal and posterior auricular vessels are then tied and the soft parts removed deeply along the with pre-auricular lymphatic gland. A very wide radical operation is then performed on the temporal bone, removing if necessary the anterior wall of the bony meatus and exposing the capsule of the temporomandibular joint. I have performed this operation upon seven hospital patients, but unfortunately it has not proved possible to ascertain the late result in any of them.

The fate of two private patients on whom this operation was performed is known to me. One was the old lady of 93 who died two years later of pneumonia, and the other the patient whose larynx had been excised. He has now died from an unknown cause, but I do know that he remained well for fifteen years after the laryngectomy and for ten years after the operation on his ear.

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PŘECECHTEL, A. (1938), *Acta oto-laryng.*, **26**, 321.

Mr. Musgrave Woodman said that he desired to speak about seven cases which had been seen at Birmingham during the period 1930 to 1938. Four of the patients were dead and three were alive and free from recurrence. Thus the survival rate was 43%, not a satisfactory figure.

The first case was a man aged 56, who was treated first by radon and later by surgical excision. He was alive and well. The second case was a man aged 54, and the interesting part of his case

was that at the time of operation he had already a growth to the middle ear and involving th Eustachian tube. He lived for two years and died following extension of the tumour into th temporosphenoidal lobe. The next case was a woman aged 57, who was treated with radon t the meatus without result ; this was followed by diathermy excision, but by the time of operatio the growth had extended to the middle ear and down the Eustachian tube. She died of extensio into the parotid region. The next case, also a fatal one, was that of a woman with an extensiv growth into the parotid. In addition to treatment by radon and diathermy excision, she wa irradiated to such an extent that the whole of the bone over the temporal region necrosed an came away, and for months it was possible to see the dura mater pulsating. The condition went on, in spite of various forms of radiation treatment, until she died from extension into the brain. Another case similar to this was that of a private patient who was alive and well nine years after the operation. He had a very extensive diathermy ; the whole of the temporal muscle, the whole of the parotid gland, and the zygoma were removed, leaving a great crater. The last case wa his most ungrateful patient, for although she had been cured of a very extensive epithelioma she complained of an intractable tinnitus which he had not been able to cure, and she said she would rather have died from the growth than continue to suffer from the tinnitus !

The analysis of the fatal cases was perhaps more interesting than the record of the successful ones. Of the four fatal cases two died of extension through the tympanic membrane into the middle ear, and two of the invasion of the parotid gland, entering the brain through the parietal region. In his experience radon, the radium tube, and the radium beam had proved almost useless. Every case was treated first by some application of radium within the external meatus. Necrosis never developed, but the treatment was very carefully controlled as to the amount of radium which might be put in proximity to the bone. The difficulty was that owing to the proximity of bone it was not possible to give sufficient radium rays in the external auditory meatus to remove the growth. In not one of the three successful cases had radium or any like agent been successful even in checking the disease. On the other hand, diathermic excision, possibly followed by prophylactic radiation afterwards, had proved successful. The excision must be as adequate and complete as possible.

Mr. F. C. Ormerod said that one case included in Mr. Scott's list of which he had some personal knowledge was operated on by Mr. Chubb in 1928 and treated by insertion of radium needles. There was complete disappearance of the tumour for one year. It then recurred, and a sleeve resection was performed, without any further radium, and the condition quite cleared up. It was now ten years since the surgical operation. The radium failed to cure the condition, but sleeve resection was effective. In another case a general in the Chinese army came for treatment with the history that for many years he had had a malignant growth in the nasopharynx. He had had it treated by radium in China, and afterwards he spent some time in Germany, where he was treated extensively with deep X-rays. Eventually he arrived in London with this growth still present and with secondary deposits in the cervical vertebræ. At the time he saw him there was an obvious malignant growth pushing through the tympanic membrane. That was possibly one of the rare examples of the progression of growth from the nasopharynx to the ear *via* the Eustachian tube. He did not know the subsequent history of this Chinese general, as he went back to China to take part in the war.

Mr. McCay mentioned a case under his care at present, showing how easily carcinomatous condition of the ear might be missed.

A woman aged 52. Aural polypi removed in 1935 ; these recurred and were again removed. In 1938 radical mastoid operation performed. Prior to operation her symptoms were deep boring pain in the ear and severe headache. Cholesteatoma was found with granulations filling the tympanum and extending into the antrum.

Subsequently these polypi recurred and were removed on three occasions, the last time being five weeks ago when the polypi were found to be very firm, fibrosed, and not at all like normal polypi. Histological examination showed the condition to be basal-celled carcinoma.

The deep boring pain in the ear had been so severe the patient had threatened suicide. She is now having deep X-ray therapy, and although she has had only nine treatments so far, there is definite relief.

The following illustrative cases were recorded by **Mr. Sydney Scott**:—

Case 1.—*Hæmangio-endothelioma of the external auditory meatus. Excised by diathermy. Condition nine months later.*

Mrs. A. S., aged 52, when she first attended St. Bartholomew's Hospital in March 1929, complaining of deafness in the right ear for twenty years and in the left ear for three months. The latter was relieved by catheterization but she continued to attend regularly for a year with tinnitus in the right ear. In September 1934 she returned to the hospital again and the left drum membrane is described as being red and bulging, and was punctured, but only blood "under pressure" escaped. It continued to bleed for a week. Four months later three "granulations" were seen in or near the left drum membrane. These appeared to coalesce and in six months appeared polypoid. Doubt was expressed whether they were inflammatory. The patient discontinued her visits for two years, and refused to have any operation until after an interval of three years, by which time a pulsating bright red swelling completely blocked the deep meatus.

Biopsy (Dr. Magnus) showed this to be a hæmangio-endothelioma. In June 1938 this was excised through a post-aural incision by means of the diathermy knife, without opening the mastoid or tympanum. The present condition shows a free passage in the meatus to the drum membrane with no sign of pulsation or granulation. The patient is deaf in both ears, the deafness being indistinguishable from that due to otosclerosis. The left drum membrane can be inflated by catheter.

Case 2.—*Squamous carcinoma of the ear, following lupus vulgaris.*

James M., aged 43, attended St. Bartholomew's Hospital under the care of Sir Charles Gordon Watson in February 1932, with an ulcer of the right ear involving the external meatus and parotid region. There was a long history of lupus treated by ultra-violet rays (X-rays) previous to the formation of a suspicious looking ulcer, which proved by biopsy to be squamous carcinoma (Dr. Robb-Smith). This was treated with 1,890 mgm. of radium, but proved intractable, and as the patient was suffering intolerable pain and insomnia, he was referred to Mr. Scott, July 1932, who excised the pinna, meatus (not the drum membrane), and parotid gland, with surgical diathermy. There was immediate relief to pain. The open wound slowly healed without being skin-grafted, and has remained healed. The external meatus is clean, dry, and the drum membrane intact. The patient has normal hearing.

Case 3.—*A malignant disease of the ear, which began thirty-two years ago.*

William H., aged 65.

Under the care of Mr. Sydney Scott, St. Bartholomew's Hospital, in February 1939.

1907: When patient was 34, he developed a rodent ulcer behind left eye above parotid gland. Treated in St. John's Hospital by X-rays. The ulcer cleared up completely and did not recur until

1931: Recurrence in the intra-orbital region. Ulceration spread to left auricle.

1934: Diathermy excision of pinna, external auditory meatus, and parotid and infra-orbital regions. Successive skin grafts to diathermy areas.

1938: Ulcer reappeared in left intra-orbital region.

1939: In eight weeks from its reappearance, it ulcerated through cheek into mouth.

1939: *Biopsy* (February): Squamous-celled carcinoma. Broder's Group III by Dr. Brewer. Pathological Department, St. Bartholomew's Hospital.

Diathermy excision of new ulcerated area into mouth by Mr. Sydney Scott.

Mr. A. McIndoe proposes whole skin graft by left temporal artery flap.

Case 4.—*A case of "malignant disease" involving the nose and the ear surviving over twenty-four years.*

Mr. C. P. This patient was shown to the Laryngological Section by Mr. W. D. Harmer in 1922 "Carcinoma of Nasal Fossa and Antrum" (*Proc. Roy. Soc. Med.*, 15, Sect. Laryng., p. 33).

1914 (May): Radical removal of growth from inferior turbinate and nasal wall of right antrum by Mr. Harmer at St. Bartholomew's Hospital. *Biopsy:* "Malignant." Sections lost.

1915 (August): Readmitted with chronic discharge of the right ear and occlusion of the meatus by a growth. *Biopsy:* "Carcinoma." Extensive operation on ear, removal of the meatus, mastoid, contents of middle and internal ear including facial nerve.

1916 (May): Lymphatic glands dissected from the right side of the neck by Mr. C. E. West.

1920 and 1921: Plastic operation for facial paralysis (temporal muscle graft, Mr. West).

1939 (February): Patient is leading an active professional life with no signs of recurrence of the disease.

Case 5.—*Malignant disease of the auditory meatus.*

Mrs. E. D. (*née* E. A.). (Not present.)

1917: Sleeve incision of the right external auditory meatus, and removal of tympanic membrane and ossicles. *Biopsy:* "Malignant disease" (Frederick Andrews).

1939: Free from recurrence. Specimens of the sections of the meatus prepared in 1917 have been re-examined by Dr. H. B. Brewer who says in his opinion "they show rodent ulcer rather than squamous-celled carcinoma as reported in 1917".

The patient still shows no sign of recurrence of ulcer or growth in the ear which is dry and clean, though she complains of deafness and tinnitus, and liability to headaches, symptoms possibly associated with the menopause.

Case 6.—*Squamous-celled carcinoma in external auditory meatus. Excised by diathermy Condition after thirteen years.*

Mrs. E. M. R., aged 47, was first seen by the late Dr. Alban Evans in August 1925 for deafness and discharge from the right ear. Dr. Evans found a wart-like growth which pathological examination showed to be a papilloma, malignant at its base. He referred her to Mr. Scott in November 1925, who found the meatus occluded by growth which was removed for independent pathological examination. Dr. Canti reported on November 10, 1925: "Sections show the structure of a squamous-celled carcinoma with cell nests. Mitosis present, not numerous. Keratinization in cell nests well advanced."

1925 (November 11): *Operation.*—Through a post-aural incision. Sleeve excision of external auditory meatus by diathermy knife. Growth seen to be attached to anterior meatal wall. The whole of the meatus from concha to drum membrane with incus and malleus were removed. The mastoid was not opened.

1926 (March): Diathermy was reapplied to a suspicious-looking recurrence, and the ear slowly healed.

1939 (February 15): The patient's husband wrote to say that his wife "is, so far, free from further trouble".

Case 7.—*Squamous carcinoma of the ear.* (Not present.)

Mr. G. A. C., born in 1859, was first seen September 26, 1924, with pain, deafness, and discharge from the left ear. There was a swelling above and around the left auricle which had been noticed for two months, and for some days a fistula had formed, about an inch above and behind the ear The patient was in a feeble state, a physical and mental wreck. However, on September 29, 1924, I performed a radical mastoid operation which was borne better than anticipated. Disease was extensive. The apex of the mastoid was eroded and isolated by growth and sequestrated pieces of brown necrosed bone removed. The bony floor of the external auditory meatus had completely disappeared and the growth had eaten into the temporomandibular joint which was completely excised. There was no trace of drum membrane or ossicles. I realized while operating that it was a case of malignant disease and sent material removed to Dr. R. G. Canti, who reported: "Squamous-celled carcinoma probably slow growing."

After-history.—In reply to inquiries Dr. Donnellan writes on February 22, 1939, to say, "the patient (Mr. G. A. C.) will be 80 to-morrow: his niece says his ear is 'absolutely all right' and apart from mental enfeeblement his physical condition gives no cause for anxiety".

Mr. Thacker Neville referring to Cases 1 and 2, asked whether Mr. Scott would perform a similarly extensive operation nowadays. He himself hardly thought such operations would be done. The patient in Case No. 1 was absolutely deaf. He further asked whether Mr. Scott would use a muscle graft, which was very difficult, or a fascia graft, which was an easier operation.

Mr. Musgrave Woodman congratulated Mr. Scott on a brilliant result in Case 2. When one was dealing with extensive malignant disease of the ear he did not think that the possibility of retaining the hearing should be regarded as a matter of the first importance.

Mr. Herbert Tilley said it had been his custom to teach students to be suspicious of malignant disease of the tympanic regions when an adult complained of deafness, deep-seated pain in the ear, and a foul, blood-stained secretion which had developed without any preliminary constitutional symptoms of infection of the middle-ear cleft.

He cited the case of a female in whom those characteristic signs and symptoms appeared five years after Mr. West (St. Bartholomew's Hospital) had performed a complete radical mastoid operation for chronic suppurative otorrhœa. The lightest touch with a blunt probe caused free bleeding from the granulations on the median wall of the antrum. The few which were removed showed definite evidences of epithelioma. Facial paralysis supervened and was followed by fatal endocranial extensions of the disease.

In 1932 a man complained of the same early symptoms and the pathologist's report on the granulations was identical with that of the previous patient. A radium-containing needle was inserted amongst them. So far, there has been no recurrence of the disease, but the posterior bony wall of the meatus became necrosed and still remains a tightly fixed sequestrum which, in no way, causes any inconvenience or discomfort.

Mr. Sydney Scott (in reply) said he had been surprised to find survivors of fifteen years. It should encourage us to treat these cases.

There was no doubt about different degrees of malignancy. One might carry out the same operation in cases which appeared to be similar, yet the results are sometimes widely different. There must be something in the nature of the growth and in the reaction of the individual to the growth which determined the result.

To answer Mr. Thacker Neville's question, the successful case of muscle graft had been done by Mr. West ; he had not done any fascia lata grafts.

As to whether one would nowadays carry out such an extensive operation as in the case of Mr. C. P. (Case 4), it would depend on the extent of the disease revealed during the operation. In operating he had followed the disease and tried to get beyond it. The patient (Case 1), Mr. Thacker Neville referred to, was very deaf long before the operation ; she had signs of otosclerosis. With regard to the choice of treatment most of the patients had been referred to him for excision by diathermy by radiologists, or his colleagues, who considered them to be unsuitable for radium treatment, and had suggested diathermy.

It was to be noticed that most of the survivors were patients with meatal epithelioma. The case of Mr. C. P. (Case 4), must be quite exceptional.

Mr. W. M. Mollison said that microscopical examination of granulations of the meatus might be misleading. A year or two ago a case was referred to him for a second opinion. The patient, a man aged 58, had had acute otitis media with much pain ; in the deep meatus were some small granulations which had been examined

and reported as malignant, and on the strength of that report the surgeon had naturally advised radical operation. For private reasons—the patient was an artist who was just then having an exhibition of his work—it was impossible for him to have the operation immediately. A fresh examination of some of the granulation failed to show malignant change, and under local treatment the middle-ear inflammation resolved and in a few weeks the patient's membrane and hearing were normal.

Mr. Sydney Scott said Mr. Mollison had referred to that curious indolent ulceration in the meatus with exposed bone which makes one suspect malignancy. He recalled one which he had seen with the late Mr. Cheatle, and he had seen a number of similar cases privately and at St. Bartholomew's, but in all of them the pathologist had excluded malignant disease. He did not think the condition Mr. Mollison had described had been referred to before.

Section of Neurology

President—J. G. GREENFIELD, M.D.

[*March* 16, 1939]

Tumours of the Lateral and of the 3rd Ventricles

By GEOFFREY JEFFERSON and HARVEY JACKSON

THE purpose of the present paper is to set on record a series of intracranial tumours which have little in common except their location in one of the cerebral ventricles. The fact of limitation to this particular site carries its own drawbacks and makes it certain not only that the total will be relatively small, but that there will be few of the same type. None the less there is need for publication of examples of tumours in the ventricles because the literature on the subject is scanty, and because there are both diagnostic difficulties and technical points of interest in their attack.

A definition of what is meant by an intraventricular tumour is necessary. In the end the term is a purely topographical one, without any uniform pathological meaning. It has much the same general implication as the term "suprasellar" or "posterior fossa" tumour. Unlike the tumours of such groups there is more possibility of gradation of position in the intraventricular series, the tumours being more inside or less enclosed according to circumstances. In the writers' view only those which lie to all intents and purposes completely within the ventricles should be called truly intraventricular. But since no tumour is ever completely unattached, bathed on all sides by cerebrospinal fluid, and since some degree of adhesion to the ventricular wall is inevitable, we have to admit a few cases of a border-line nature. It is, however, not enough that a tumour should make a salience into the ventricle whilst the main mass is outside in the hemisphere. Examples of such pseudo-ventricular tumours will be given for comparison. This reservation removes a certain number of examples, but even these are not very common. It is much the more usual thing for a tumour to shift the ventricular systems as a whole, either by reason of its own bulk or with the aid of concomitant œdema, and at the same time to obliterate or reduce to a mere slit a ventricular horn. A local filling defect, a crescentic or rounded shadow imposed on the ventricular outline, is sufficiently unusual to excite comment but is not enough to certify that the tumour will be chiefly or wholly intraventricular.

A topographical grouping such as this has certain advantages both for the clinician and the pathologist, but it is to the surgeon in particular that these tumours make their appeal because they call for certain modifications in his more usual operative approach. They have, too, a special interest for the radiologist, for they present uncommon and sometimes difficult ventriculographic pictures.

TYPES OF TUMOUR

The ventricles are lined by a special cell layer, the ependyma, and into them all the choroid plexuses with their specialized covering project. The plexuses are contained within the fringes of the tela choroidea, and all three structures, ependyma, plexus, and tela, may, on occasion, give rise to their own specific tumours. Outside the ependymal lining lies a layer of fibrillary neuroglia from which also may originate

a tumour which necessarily comes to bulge into the ventricle and to produce its effects, as do those in the 4th ventricle, not by local neural dysfunction but by interfering with the circulation of cerebrospinal fluid. Further out still lies the more ordinary neuroglial tissue, the tumours of which almost invariably deform the ventricles and only rarely make prominences into them of greater or less size according to the shape of the tumour and its extent. Ependymal rests have long been known to lie close alongside the ventricles and to be the possible starting point for cysts or solid tumours which can come to embarrass, if not to occupy, the ventricular cavities. Moreover,

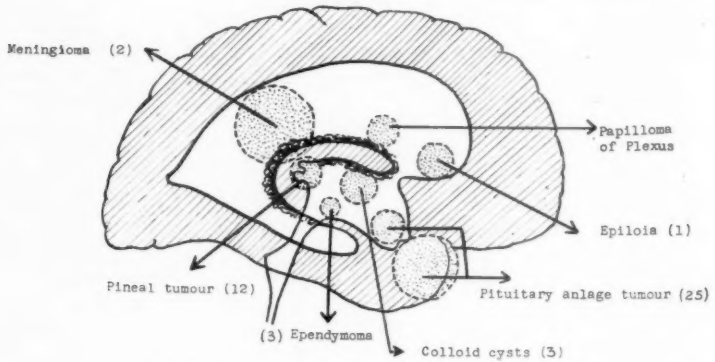

FIG. 1.—Sites of the tumours in the present series.

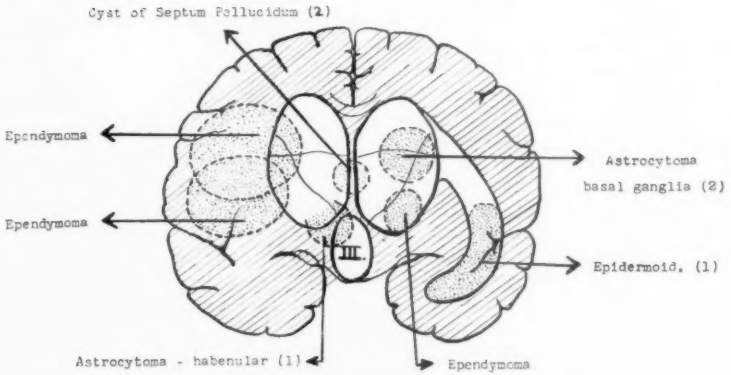

FIG. 2.—Sites of the tumours in the present series including some pseudo-intraventricular tumours.

the basal ganglia lie close by and, as we shall see, the inoperable gliomas of these structures can throw ventriculographic shadows strongly resembling lesions of a more benign type. We shall deal with this question in its proper place. Lastly there are three structures closely related to the ventricles and producing tumours which must invaginate into them. These are the paraphysis in the velum of the roof of the 3rd ventricle, the pineal organ, and the pituitary stalk and tuber. The colloid cyst which derives from the first named is one of the tumours which most perfectly fulfils the anatomical requirements of intraventricular situation. It is

inert, its secretion leads to no physiological derangement, it lies as completely within the cavity of the 3rd ventricle as a tumour could that was not free from all attachments, it produces no constant localizing neurological signs, its effects are the result of cerebrospinal fluid obstruction alone, its diagnosis is ventriculographic. The matter is otherwise with tumours of the pineal organ and of the pituitary anlage, the so-called craniopharyngiomas. It is true that the development of neoplasms and cysts from these structures is usually in an intraventricular direction, but in order that the present paper shall be kept within bounds these two groups will be touched upon very briefly. It seems to us that they have interests quite apart from their intraventricular projection, though, to be sure, the fact of it has no little bearing on both symptomatology and on surgery. One example of pituitary anlage tumour will be described because the intraventricular location was the dominant feature of the story and because the rest which gave it origin was tuberal. We believe that although the correct approach to many of these suprasellar cysts is transventricular, even when there is a considerable quantity of tumour in the sellar region, these lesions scarcely come within the meaning of the true intraventricular tumours. But they almost do so, and can indeed be used to illustrate the general meaning of the term. Here we have a lesion which often has but a small part beneath and outside the brain in the chiasmal region and a very large cystic part bulging up into the 3rd ventricle. There it rises so high that it commonly obstructs the foramen of Monro. We cannot exclude all these cysts from an intraventricular title on the grounds that they may be covered by an almost indistinguishable film of tuberal tissue which they have carried with them as they increase upwards in size. If they are to be excluded it will be because the main mass is outside the ventricle. When there is none, as in our case here described, they must be accepted as intraventricular. But probably the chief reason for exclusion is that the pituitary anlage (or pituitary duct) tumours form a well-defined group which are best described and best thought of under their own special designation.

Two cases of septal cysts and two intraventricular astrocytomas occurred, but none of the oligodendrogliomas which, as Greenfield and Robertson (1933) showed, can exist in the ventricle. One invasive oligodendroglioma of the 3rd ventricle occurred, but it is not included as it was not sufficiently local. The patient had an irregular pulse, pyrexia and asthma, dating from the onset of clinical signs. The question of autonomic disturbance and hypothalamic invasion will be discussed later. We have no example of an intraventricular neurocytoma, two of which were reported by Kernohan, Learmonth and Doyle (1932).

In brief, there are five tumour types which are clearly and unmistakably intraventricular: (1) the choroid plexus papillomas, (2) the meningiomas of the tela choroidea, (3) the colloid cysts of the paraphysis, (4) the epidermoids, (5) a few gliomas, originating either from the ependyma or the extra-ependymal neuroglia around the ventricles. Pineal and pituitary anlage tumours commonly bulge into the ventricles (as may the suprasellar extensions of pituitary adenomas), as do also gliomas of the basal ganglia, but these groups are best considered under their own titles.

Literature

There is no doubt that we owe to Dandy our awareness of the topographical group under discussion. In his two monographs devoted to tumours of the lateral and 3rd ventricles he illustrated very fully the deformations that they occasion and described the surgical steps best fitted for their attack. He gives a tabulated analysis of the isolated cases which had been published up to the dates of his books. Since that time several papers have appeared, some the records of single cases, some the records of groups. The most important addenda are to be found in Cushing's book on the meningiomas, in the monograph on the hypothalamus by Clark, Beattie, Riddoch, and Dott, and in papers by McLean, Stookey, Kessel and Olivecrona, Gardner, Allen

and Lovell, Fincher, Schmidt, Saralegui, Tönnis, Arce and Balado, Vonderahe and Abrams, and Faber. The ventriculographic side has been added to by Twining, Lysholm, Johnson and List, Davidoff and Dyke, and Askenasy.

Material

The accompanying table gives in brief form the pathological types of the series on which this paper is based.

A. *Lateral ventricle :*

Meningiomas	2 cases
Choroid plexus tumours	1 case
Epidermoid	1 case
Local astrocytoma	2 cases
Ependymoma	3 cases
Epiloia	1 case

B. *3rd ventricle :*

Meningioma	1 case
Colloid cysts	3 cases
Epithelial cyst	1 case
Pituitary anlage	1 case
Ependymoma	3 cases
Cyst of septum lucidum	2 cases

C. *Pseudo-tumours of the ventricles :*

Chiefly tumours of the basal ganglia.
Two examples will be selected.

In addition there were 23 out of 25 cases of congenital pituitary origin which indented the 3rd ventricle, and 12 pineal tumours.

The sites of the tumours have been indicated in figures 1 and 2 (p. 60). Most of the pseudoventricular tumours are shown in the anteroposterior view ; in the text that follows they are scarcely more than mentioned, for the sake of reasonable brevity. Fifteen cases will be described.

Intraventricular Meningiomas (Three Cases)

We have three examples of these rare tumours in our series. The first lay in the left lateral ventricle, and proved to be a rather massive tumour, 165 grm. in weight. There was a ten-year history.

Case 1.—M. H., female, aged 29, was in the National Hospital under the care of Dr. Macdonald Critchley, referred by Mr. Nicholson Lailey.

Ten years before she suddenly had a " fit " in which she dropped unconscious in the street ; she was generally convulsed, bit her tongue, and voided urine. At weekly intervals during the next three years she had similar attacks, without warning and without lateralizing phenomena. For a matter of about half an hour subsequent to the attacks she felt a little dazed and was unsteady on her legs. A period of four years then elapsed, free from attacks, but headache continued, awakening her in the mornings. They were frequently associated with vomiting. Three years before her attendance at hospital, during the later stages of pregnancy, she had a further fit, and from that time she noticed a deterioration of vision, evidenced first of all by the appearance of black spots before her eyes, to be succeeded by general loss of visual acuity. For a period of a week some nine months prior to hospitalization she became temporarily completely blind ; during this time she had to grope her way about the house. Vision improved but she was unable to read or sew. With the onset of visual failure the headache assumed occipital and suboccipital distributions and was accentuated by stooping and straining. She complained also of giddiness for several months, by which she meant an unsteadiness or light-headedness on stooping. Her speech had never been affected, but she was left-handed. For something like twelve months preceding admission she complained of peculiar attacks of numbness in the left side of her body, generally induced by sudden movement.

She was a healthy woman, well nourished, a little slow mentally but not intellectually defective. Visual acuity $\frac{6}{6}$ R. and L. Chronic papillœdema with consecutive atrophy present in both eyes, the swelling a little more marked on the left. Visual fields showed a homonymous quadrantic defect in the right lower field. There was fine, sustained nystagmus on looking to the extreme left. Slight right-sided facial weakness, more obvious on emotional movement. Abdominal reflexes were depressed on the right, the right plantar reflex was doubtfully extensor, the left a definite flexor. Her cerebrospinal fluid was under a pressure of over 300 mm. on lumbar puncture, the W.R. was negative, and the total protein content was 0·120 mgm.%. Ventricular fluids showed a protein content of 50 mgm. on the right and 180 mgm. on the left. Although there

ere definite localizing signs and evidence of raised intracranial pressure, the precise nature and relationships of the tumour remained uncertain. It was therefore deemed advisable to carry out ventriculography before embarking on a major cranial exploration. Ventriculograms showed large filling defect in the left lateral ventricle (*see* fig. 4). The fluids obtained by ventricular puncture proved of further significance in their protein contents, and additional evidence was forthcoming in the location of a resistant structure on the left side on the insertion of the cannula.

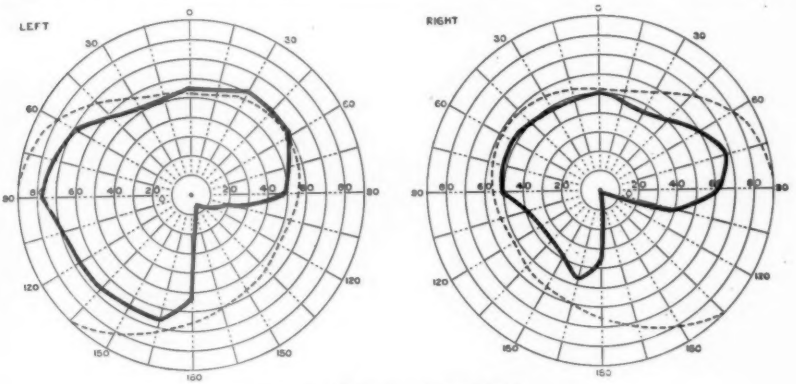

FIG. 3. (Case 1).—Visual fields.

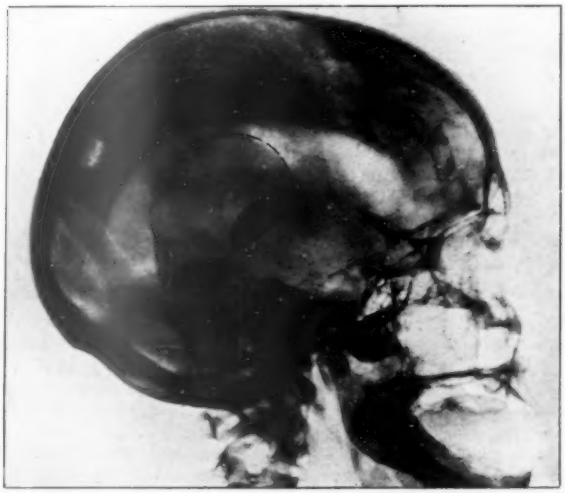

FIG. 4 (Case 1).—Ventriculogram showing filling defect, left intraventricular meningioma.

At operation (H. J.) a large mass was encountered approaching the cortex at a minimum depth of about 1 cm.; the overlying cortex was incised and a large tumour enucleated from the left lateral ventricle. The tumour was intimately attached to the choroid plexus, which was secured with clips. A portion of the plexus was removed with the specimen. This is well illustrated in the accompanying sketch (fig. 5) made from the excised tumour. Histologically it was a fibrous

meningioma with occasional psammoma bodies dispersed sparsely (*see* fig. 6). The patient remain well four years later.

Little clinical evidence was available for the location of this tumour within the ventricula system. There is some tendency at intermittency in the history. It is particularly worthy c note that unsteadiness of the legs was noted to follow on her attacks, as some observers hav described weakness of the lower limbs in association with 3rd ventricle tumours, especially th colloid cysts. Cushing suggests that lateral ventricle meningiomas present five signs, (1) pressur signs with headache that tends to be unilateral, (2) contralateral homonymous hemianopia, ofte

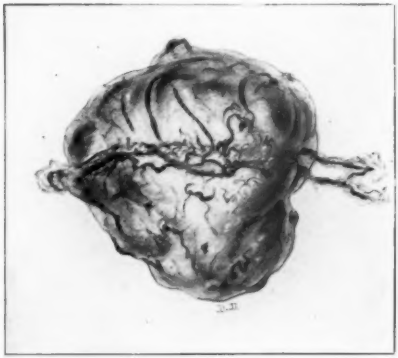

FIG. 5.

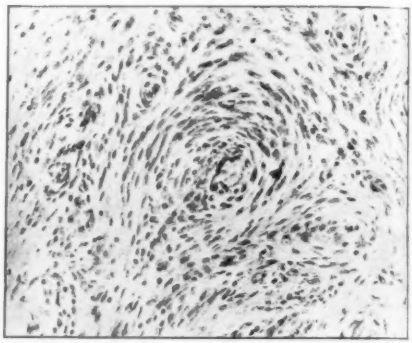

FIG. 6.

FIG. 5 (Case 1).—165 grm. meningioma removed from left lateral ventricle. The choroid plexus is attached to the tumour.

FIG. 6 (Case 1).—Histological section of the meningioma.

bisecting the macula, (3) contralateral sensorimotor hemiparesis more marked as regards sensation than movement, (4) symptoms suggesting cerebellar involvement, (5) almost invariably paralexia when the tumour is on the left side. But we must add another important thing, the time factor. It is the evolution of these signs over a longer period of time than is consonant with the actual physical signs that will make the clinician think that the tumour must lie in a sheltered position for there to be so much to say and so little to see. One must admit that the histories of most of the reported cases are considerably shorter than in the above case, but as a generalization the truth of the addendum remains.

The second case filled the 3rd and extended into the lateral ventricle, a particularly rare situation.

Case 2.—*Intraventricular meningioma filling the 3rd and part of the right lateral ventricle.*

M. A., a frail girl aged 11, was admitted to the Neurosurgical Service of the Manchester Royal Infirmary May 19, 1937, referred by Dr. Tinto of Bolton, complaining that she had not felt well for eighteen months. She had had a number of attacks of headache and sickness but as each soon passed off they were diagnosed as bilious. She was ill thus for a day on several occasions with pain at the front and back of the head. There was nothing else of significance in her history apart from the steadily increasing frequence of the attacks. On examination there was bilateral papillœdema, with general contraction of the fields, and slight left-sided pyramidal signs. In addition she had a coarse, cerebellar type of nystagmus on lateral fixation, but it was not well sustained. Her gait and co-ordinated movements were excellent. The pupils reacted to light and accommodation. X-rays showed a hydrocephalic type of skull with ballooning of the temporal fossæ.

There was no abnormal intracranial calcification. The lumbar cerebrospinal fluid contained 200 mgm. of protein. A suggestive sign had been hypersomnia, in the late afternoon she would become drowsy and was difficult to rouse, but once properly awake she was quite bright. Soon she would feel tired and drop off to sleep again.

Diagnosis was uncertain and the patient was kept under observation for some time. She became occasionally incontinent of urine and fæces. However, a posterior fossa exploration was carried out on May 29, 1937, with negative findings, by one of G. J.'s assistants, who felt that she would not stand ventriculography. Intraventricular pressure was between 900 and 1,000 mm. of water. Tonsillar herniation was present. She appeared to be making a smooth recovery when she died suddenly on the sixth post-operative day. At necropsy by James Hardman a large fibroblastic meningioma was found to be moulded into the 3rd ventricle and to have separated the anterior pillars of the fornix which wound round the lateral surfaces of the tumour (*see* fig. 7). It extended into the lateral ventricles behind the foramina of Monro which were reduced to slits. The tumour was lobulated, the lobulation corresponding to the parts of the tumour lying in the

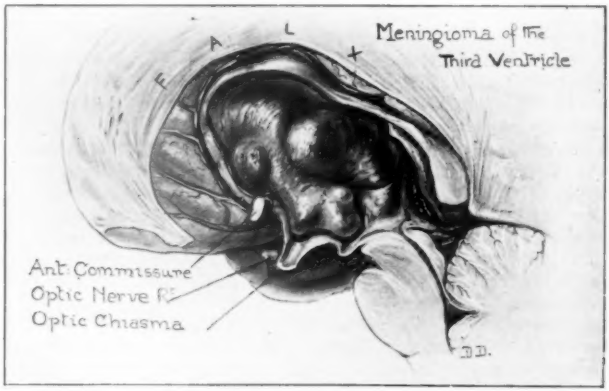

FIG. 7 (Case 2).—3rd ventricle meningioma.

FIG. 8 (Case 2).—Perdrau stain of fibroblastic intraventricular meningioma.

different ventricles. This could only have occurred by the development of the tumour in the velum interpositum in the roof of the 3rd ventricle and by dissection up into the septum pellucidum and then laterally above the choroid plexus of the lateral ventricles. The 3rd ventricle was completely filled by the tumour and it extended into both lateral ventricles, more especially into the right. The corpus callosum was missing in its anterior third. Even at necropsy the tumour was very difficult to dislodge and at operation would have been impossible. It is curious that hypersomnia should have been the only hypothalamic sign; there was no polyuria or irregularity of respiration or of temperature. Nor had the upper surface of the chiasma been indented, for the fields showed no patterned defect. Histologically it was of extremely fibroblastic type (fig. 8), as seems to be the rule with tumours in these locations. Judged by the manner in which it extended and altered the normal anatomy of the corpus callosum and fornix

it must have grown very slowly and probably began many years ago. It might even have been a congenital tumour, for it is the fact that intraventricular meningiomas have been discovered in children of very early age.

Since this paper was delivered a third intraventricular meningioma has been encountered.

Case 3.—*65-grm. meningioma in the body of the left lateral ventricle.*

A. J. M., female, aged 56, referred by Mr. McCulloch of Bradford with chronic bilateral papill-œdema and no localizing signs. Some nine months ago she had consulted Mr. McCulloch on account of transient obscurations of vision, and he observed a suggestion of a right-sided homonymous hemianopia, but it disappeared and the fields were normal in May 1939 save for slight enlargement of the blind spots. Vision $\frac{6}{9}$ in both eyes. At no time had she had headache. During the last five months she had had spasms of the facial musculature on the left side, similar to those which may occur as a result of acoustic neurinomas. Hearing and vestibular tests gave normal responses. Lumbar cerebrospinal fluid pressure was 210 and the protein 35 mgm. per 100 c.c. Bilateral ventricular punctures were made; the fluid from the right was clear, protein 10 mgm., that from the left canary yellow, protein 2,000 mgm. per 100 c.c. 2 c.c. of thorotrast were injected into the left ventricle under the impression that the fluid came from a gliomatous cyst. X-rays showed the thorotrast outlining the dilated occipital horn of the left lateral ventricle and a small part of the trigone of the lateral ventricle. In front of this was a crescentic shadow convex backwards. Evidently a tumour occluded the ventricle completely so that cerebrospinal fluid was loculated in the posterior end. This is an extremely rare happening and some have wondered whether it is possible. There was no doubt about the correctness of the observation in this case; further X-rays three days later showed that the thorotrast had not moved forwards to outline any more of either tumour or ventricle. On 17.6.39 an intraventricular tumour weighing *circa* 65 grm. was successfully removed by transcortical incision (G. J.). The choroid plexus was firmly adherent to the external surface of the tumour which was jammed into the ventricle and could only be removed by traction sutures after its interior had been gutted by suction and endothermy. There was a transient apraxia and slight confusion of words after operation, but not the severe reactions that have been recorded after the removal of some of these tumours.

Histologically the tumour was reported by Dr. Eugen Pollak to be a fibroblastic meningioma.

In Cushing's monograph will be found two cases of his own and 17 from the literature of meningiomas in the lateral ventricles. He and Louise Eisenhardt attribute the origin of these tumours to the meningocytes in the tela and only to the choroid plexus if they are particularly free in the ventricle and psammomatous. The freedom of a meningioma within the ventricle must depend on its size and on the whole a velar origin seems the most likely. Cushing and Eisenhardt published two beautiful sections of meningocytes and psammoma bodies in the normal adult velum interposition (tela choroidea). Even if a small and mobile meningioma were found by chance within a ventricle it would scarcely settle the site of origin, for it might have started from cell rests in the velum contiguous with the plexus. It may be added that Busch, in recording five examples of intraventricular meningioma which occurred in a series of 502 cases from the Danish Neurosurgical Clinic (a high proportion) finds himself in the same difficulties as to the derivation of his tumours and cannot place them clearly in the suggested groupings.

Colloid Paraphysial Cysts (Three Cases)

Of all intraventricular lesions the colloid cysts, which originate in the paraphysial relics in the roof of the 3rd ventricle as suggested by Sjövall in reporting the eleventh case in 1910, are the best known. They possess all the attributes of truly intraventricular tumours both in gross morphology and in their physiological effects. Furthermore, they are remarkably similar in size, situation, and appearance, from one case to another, and of all intraventricular tumours lend themselves most readily to standardization clinically, operatively, and pathologically. Thirty-one cases were on the records prior to Dandy's publication of five examples in 1933. A number

of isolated cases have since been published and four important series—Stookey (1933), Davidoff and Dyke (1935), Kessel and Olivecrona (1936), and McLean (1936). The present writers are able to add three more. The general picture of these cases is now well known. They produce little in the way of local symptoms, but by obstructing the outflow of cerebrospinal fluid through the interventricular foramina lead to bilateral hydrocephalus, vomiting, headache, and papillœdema. The symptoms are notoriously intermittent for the block at the foramina of Monro is seldom permanent and the patients sometimes, but not always, have observed that certain postures of the head can make the headache either better or worse. The hydrocephalus is, in general, intermittent, and in those cases, and they are not few, in which a rapid if not a sudden death has supervened, no doubt the outflow of cerebrospinal fluid has been recently completely prevented by the cyst. Whether these variabilities are due to movement of the cyst or to local alterations in vascularity is not yet determined. Observation at operation would suggest that the unopened cysts are not particularly free to move about. Nor, for that matter, do the extremely viscid colloid contents (of a degree unequalled in any other cyst) suggest that there are alterations in actual volume due to changes in its interior. We believe that variations in the state of the choroid plexus, aided possibly by slight movement of the cyst, account for the intermittency of the foraminal obstruction and therefore of the symptoms.

The cases will be given in skeleton outline only, for they had no special features to distinguish them from those so often recorded.

Case 4.—M. R., female, aged 45, admitted to the National Hospital under Dr. Macdonald Critchley, April 1936. Seven years' history of intermittent attacks of headache and vomiting with occasional major epileptic seizures. Transient papillœdema observed after the first attack. Recurrent psychotic delusions of persecution which were probably not causally related as they

FIG. 9 (Case 4).—Histological section of paraphysial cyst wall.

returned at times after the successful removal of the cyst on May 28, 1936 (G. J.). Diagnosis by ventriculography. Patient well three years later. A section of the wall of the cyst is shown in fig. 9. This case was shown at a clinical meeting of the Neurological Section (*Proc. Roy. Soc. Med.*, 1937, **30**, 850 ; Sect. Neurol., 54).

Case 5.—K. T., aged 31, was referred by Dr. Kiep on account of bilateral papillœdema. He developed severe nagging headache in February 1937, attributed by the patient to snow blindness after skiing. Generally well for the next twelve months except for hypersomnia, a pronounced

feature over a period of many years. He was well able to carry on with his business until the headache returned after another holiday at the winter sports in Switzerland. The headaches this time were much worse and paroxysmal, lasting generally only ten to fifteen minutes. When the headache was present he looked to be in a stupor. The pain might radiate to the back of the head and into the neck. For a period of two weeks he had attacks of a numb feeling in the legs lasting for five minutes. It needed a considerable effort to lift the feet at these times and he

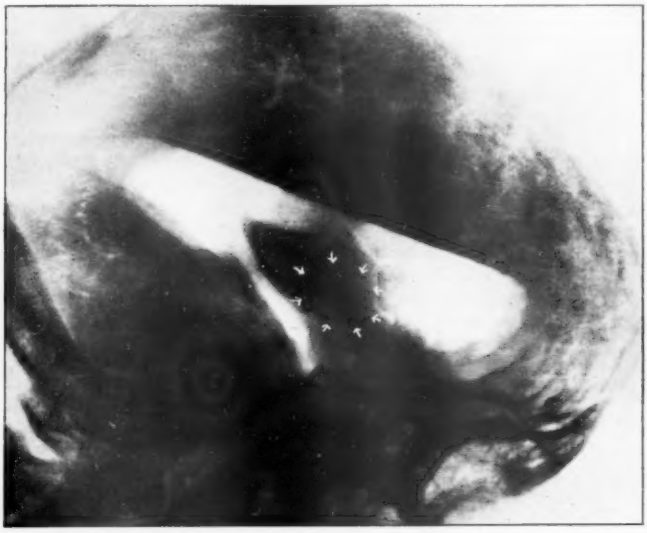

FIG. 10 (Case 5).—Ventriculogram of colloid cyst. Note filling defect immediately behind foramen of Monro and small size of the thalamic shadow.

walked as if drunk. Once he stumbled and fell. Dr. Elwell, his own doctor, referred him to Dr. Kiep, who found bilateral papillœdema. Neurological examination was negative except for the papillœdema. Lumbar puncture protein—35 mgm.%. There was no postural relief for the headache, which would sometimes disappear for two or three days on end. Ventriculographic diagnosis (fig. 10). Successful removal, by usual transventricular approach, on May 5, 1938 (G. J.). Patient well one year later.

Case 6.—G. H., aged 52, was in the National Hospital under the care of Dr. Hinds Howell. She showed marked mental disturbance, in consequence of which she was unfit to give a detailed history. Her husband had noticed six months before that she was slow in walking, with a steady tendency to get worse. She had been found by a neighbour five months earlier crawling around the garden as she found herself unable to get up after falling. At intervals she fell suddenly, without losing consciousness, owing to a sudden tendency for her legs to give way. A fortnight after the onset of these attacks of weakness, she had an attack in which she was unconscious for several minutes in which both sides of her face twitched but no associated movements of the arms or legs took place. This attack was followed by continuous frontal headache which persisted for a week, and frequent vomiting occurred on taking food. Headache continued from that time ; it was of frontal distribution. Mental change was noted from the onset and was progressive. She gradually became more stupid and for five months before attending hospital was unable to look after her household. Her memory became poor, but on the whole she was happy and placid ; a rather unusual state for her as she previously had been easily depressed. She had no insight into her condition, minimized her complaints and, except on rare occasions, always maintained that she was " quite all right ". Speech normal. No giddiness or tinnitus. Her

sight had been failing for six months before treatment was sought. For eighteen months she had been a little drowsy.

On examination.—A very obese woman who lay motionless in bed, slow and lethargic in manner, disorientated in space and time, placid, contented, and peaceful, inattentive, but took her food well. There was slight ptosis on the right, and low-grade papilloedema without hæmorrhages (2 D). She had a right lower facial weakness on both voluntary and emotional movement; the right arm was spastic, the spasticity being a plastic extrapyramidal type. Grip was slightly weak, also dorsiflexion of wrists, more particularly on the right. There was marked rigidity of the right lower limb. Reflexes sluggish but equal. Left plantar weak extensor. She was incontinent of urine and fæces. Lumbar puncture revealed a cerebrospinal fluid pressure of over 300 mm. Total protein 0·035 mgm.%. There was a bony boss present over the left frontal region.

The combination of pyramidal signs with the presence of a bony boss seemed adequate evidence for the diagnosis of a left frontal lesion, and in accordance therewith a left fronto-parietal osteo-

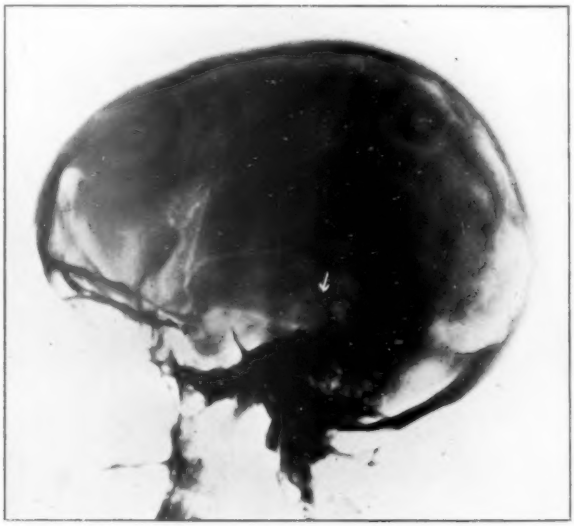

FIG. 11 (Case 6).—X-ray of skull showing depression of pineal shadow in hydrocephalus produced by colloid cyst of 3rd ventricle.

plastic flap was turned down (H. J.). On reflection of the bone, however, no evidence was forthcoming of underlying neoplasm, and for possible verification a cannula was inserted through a small perforation in the dura; as a result a large anterior ventricular horn was located. The dura was not opened up, but the flap replaced pending ventriculographic examination. A few days were allowed to elapse, then ventriculography was carried out. The ventriculograms demonstrated the presence of a block in the region of the foramina of Monro with non-filling of the 3rd ventricle, but the condition of the patient was such that further intervention was considered unwise at that time and exploration was deferred. However, the patient never improved sufficiently for this to be carried out and died suddenly before any further attempt could be made.

A point of especial interest is to be noted in the unusual amount of depression of the calcified pineal shadow, visualized in the plain radiograph of this case (fig. 11). This displacement of normal structures probably accounts for signs suggesting implication of the tegmental region, especially

when such resultant signs are observed to be of varying intensity (e.g. disturbances of the pupils, lids, and movements of the eyes).

Fig. 12 illustrates the condition found at autopsy.

This case illustrates well that symptom of weakness of the lower limbs (cp. also Case 2) which is described by some observers as associated with 3rd ventricle lesions. The depression of the pineal gland is an important finding, as this would otherwise have been considered an unlikely association of tumour formation in the anterior portion of the 3rd ventricle. Drowsiness was noted over a considerable period, but could hardly be suggested as an outstanding feature.

The diencephalic signs which can accompany these cysts will be mentioned again in a later section. It is now the general consensus of opinion that the cysts are derived from the paraphysis (McLean, 1936) and Bailey refers to them as " neuro-epithelial ", a correct enough title. Kessel and Olivecrona consulted Hochstetter on the embryological derivation of the cysts, but he was non-committal. They were

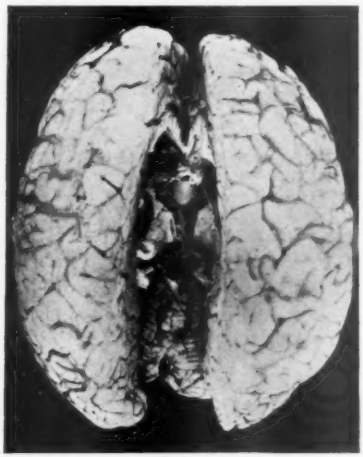

FIG. 12 (Case 6).—Dorsal view of colloid cyst of 3rd ventricle.

led to this because of the scepticism of Foerster and Gagel. It is quite clear that the older idea that they arose from the choroid plexus must be incorrect, for cysts of this kind do not occur on the plexuses in the other ventricles. The content of these cysts is quite unlike that seen anywhere else ; it is so extremely viscid that it can scarcely be lifted with average suction power. When stained it has no structure. A further point suggesting that these cysts arise from a specific organ is the constancy of their position. Hochstetter has seen minute cysts in the roof of the 3rd ventricle in sections of embryos but they must disappear later.

It seems, however, that other cysts than colloid can develop from the 3rd ventricle roof. Whether they are the same as the colloid cysts is uncertain. We can do no more than call them dermoid or epidermoid. We have one example to illustrate this kind. Another similar one will be found in the paper by Davidoff and Dyke, who speak of the cheesy yellow contents of their specimen, so unlike the colloid of the other better-known type.

EPITHELIAL CYST OF THE 3RD VENTRICLE

In this case an epithelial-lined cyst presented within the 3rd ventricle arising in the roof and protruding into the floor of the lateral ventricles. The site of origin was posterior to that in which the paraphysial cyst is usually found, and the contents were more inspissated in parts. The actual pathology would appear doubtful, for while the histological sections simulate some of the recorded cases of colloid cysts, the appearances at operation make it of dermoid origin.

Case 7.—E. G., aged 51, a patient under the care of Dr. Gordon Holmes at the National Hospital. Four years before coming to hospital headache commenced; it was localized to the frontal and temporal regions, was accentuated on stooping or looking upwards, and inclined to come on in the evening. About the same time he noticed that the left eye was turning outwards. On two occasions the eye was operated on for correction of the squint, each time, however, the deviation recurred. For three years he had been subject to attacks in which he felt weak all over, his

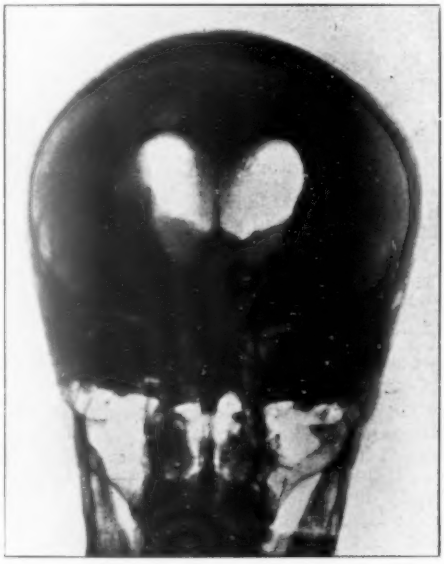

FIG. 13 (Case 7).—Ventriculogram of epithelial cyst projecting upwards from the 3rd ventricle.

legs staggered, then he fell backwards and lay helpless on the ground. In the first place there was no associated loss of consciousness, but later on he failed to recollect having had attacks.

On examination.—A healthy individual of normal mentality. Visual acuity ⅔ R. and L. Optic discs were a little pale with blurred margins, about 2 D of swelling but no hæmorrhages or exudate. There was usually an external strabismus of the left eye though at times the axes of the two eyes were parallel, but convergence of the left eye was impossible. Otherwise ocular movements were normal. The pupils were regular and equal, reaction to light was rather sluggish. No nystagmus, ptosis, en- or exophthalmos. Reflexes present and equal, plantars flexor.

Lumbar puncture revealed a cerebrospinal fluid pressure of 300 mm. The fluid contained a total protein of 0·050 mgm.%.

Dr. Holmes suggested that the condition of the eyes was compatible with a tumour of the 3rd ventricle. Ventriculographic examination revealed absence of filling of the 3rd ventricle and the presence of a circumscribed filling defect bulging upwards into the floor of the lateral ventricles in the middle line (fig. 13). Exploration of the right lateral ventricle by the right

frontal transcortical route (H. J.) revealed a bulge of the ventricular floor at a site corresponding with the radiographic deformity. The tumour lay a matter of half an inch or so posterior to the foramen of Monro, elevating the floor of the lateral ventricle and protruding upwards into the substance of the septum pellucidum. The diameter of the mass would be about three-quarters of an inch in both anteroposterior and lateral directions. Incision into floor of the ventricle over the prominence revealed a yellowish, elastic mass, containing inspissated material simulating the contents of an ordinary sebaceous cyst intermingled with a viscid, mucoid-like substance.

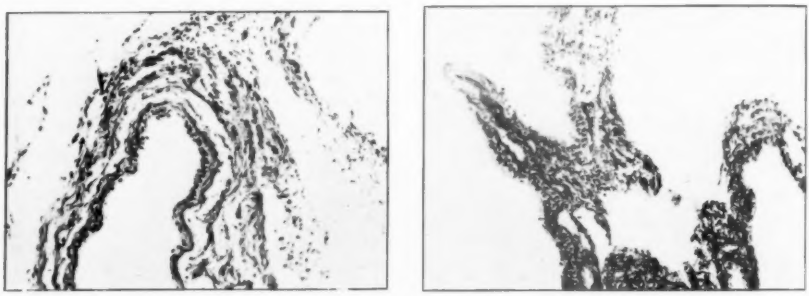

FIG. 14 (Case 7).—Photomicrographs of the wall of epithelia cyst of 3rd ventricle showing columnar nature of determining cell and tendency to papilliferous intrusions.

Evacuation of the cavity was followed by extirpation of the capsule with the formation of a large communication between the lateral and 3rd ventricles.

Histologically the wall of the cyst consisted of several layers of connective tissue lined by a single layer of columnar epithelium (fig. 14). In parts papillæ were present, formed by vascular projections of connective tissue. A few small cystic divarications were seen in the cyst wall.

This case presented several points of significance; looking upwards accentuated the pain; weakness of the lower limbs was described; peculiar disturbances of ocular movements played an important part in the history.

In this series of cases several symptoms and signs of importance are mentioned. Intermittency of history is apparent in two patients, weakness of the lower limbs in four, postural effects on pain in three, and disturbance in ocular movements of unusual character in one.

PAPILLOMA OF CHOROID PLEXUS

Only one example of this as a lateral ventricle lesion occurred in the series. We have no example in the 3rd ventricle, though there have been six in the 4th. The last are being reported on separately by W. E. Kershaw. The tumours are slightly rarer in the lateral ventricles than in the posterior fossa in spite of the comparatively great extent of the plexuses in the former situation.

Case 8.—J. T. H., aged 26, gave a three months' history of severe pains in the head and of vomiting as often as four or five times a day. The pain was retro-ocular, vertical, and in both temples. His neck was stiff when the headaches were at their worst. Latterly his vision had become misty for a few seconds but then was generally clear. He was often a little unsteady in his gait. There had been no fits. Examination showed bilateral papillœdema, two diopters, with normal visual acuity and fields. Pupillary reactions were normal. Nystagmus of rapid type, not very pronounced, on deviation of the eyes to both sides. On the motor side there was tremor of the left hand and the tendon reflexes were extremely active, especially on the left side. The plantar reflexes were flexor, the abdominals absent. A right-sided subtemporal decompression was done on 17.11.31 as a palliative measure. He was relieved of his discomforts for eighteen

months when he commenced once more with paroxysmal headaches and pain in the neck. This was so bad at times that he could not turn in bed. His unsteadiness returned, and during the next two months his vision deteriorated. He was admitted to the Manchester Royal Infirmary and on June 1, 1933, the ventricles were punctured. 35 c.c. of yellow fluid were obtained from the right ventricle, 5 c.c. of clear normal fluid from the left. The yellow fluid contained 1,800 mgm. of protein. Ventriculograms were faulty but indicated an enlarged right ventricle with a filling defect anteriorly and with displacement to the left. On June 27, 1933, a right frontal osteoplastic flap was turned down under local anæsthesia. The cortex was flattened, thin, and slightly yellow-stained. Puncture withdrew yellow fluid at a depth of less than 1 cm. The cortex was incised and the cavity found to consist of the widely distended lateral ventricle. After sucking it dry

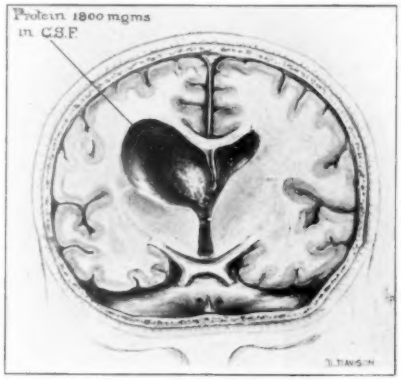

FIG. 15 (Case 8).—Diagram of papilloma of the choroid plexus, right lateral ventricle.

the usual landmarks were visible except the choroid plexus which was replaced by an elongated dark brown slightly villous tumour (fig. 15). This was punched away and its remains extirpated with the endothermy loop. The foramen of Monro which had been obscured by the tumour now came into view. It had been blocked by the tumour with the production of a unilateral hydrocephalus. A complete removal of the tumour was effected and five and a half years later the patient is completely well. A somewhat similar case has been reported by Tönnis. In Van Wagenen's successful case (1930), remarkably similar to that just recorded, even to its two-stage removal, the xanthochromic cerebrospinal fluid from the left ventricle, which harboured the tumour, contained 2,062 mgm. of protein, that from the right 225 mgm.

CYSTS OF THE SEPTUM PELLUCIDUM (TWO CASES)

No example of a cyst of Verga's ventricle has occurred as a clinical entity in the series. On the other hand, a cyst of the septum pellucidum was met with on two occasions, and a solid tumour on a third. In the second a congenital cyst was present in the septum of a four-year-old girl operated upon successfully by the transventricular route for an upward extending pituitary anlage cyst. It may, in that case, have added to her disability, but was not so clearly as in the case which follows, the clinical history of which we owe to Dr. Purdon Martin. In the third case a globular astrocytoma sprang from the septum.

Case 9.—*Gliomatous cyst of septum pellucidum. Unilateral hydrocephalus (left). Approach through corpus callosum.*

M. L., female, aged 27, was admitted to the National Hospital under Dr. Purdon Martin. Her relevant history began with two six-month periods of amenorrhœa and great menstrual

irregularity dating back over five years. She had felt very tired and unready for work for four years ; this was not her nature and it worried her. For thirteen months she had had increasingly severe headaches, and for two months she had had fits. These convulsive seizures were not accompanied by loss of consciousness and affected the right side of her body. They came every other day and could often be stopped by pressure, as by squeezing the right arm against the wall of a room or of a street. There was no mental deterioration. Vision in the left eye had been getting worse for the past two months. There was nothing for special comment in her appearance or demeanour or on general examination. Visual acuity R. $\frac{6}{18}$; L. less than $\frac{6}{60}$; bilateral low-grade papillœdema ; there was a central scotoma in the left eye measuring about 15°, and one of 3° in the right eye to a 1 mm. object but not absolute as she could still read (fig. 16). The abdominal reflexes were more exhaustible on the right, but no other clear evidences of pyramidal involvement could be elicited. X-rays of the skull showed a rather large sella, but the dorsum

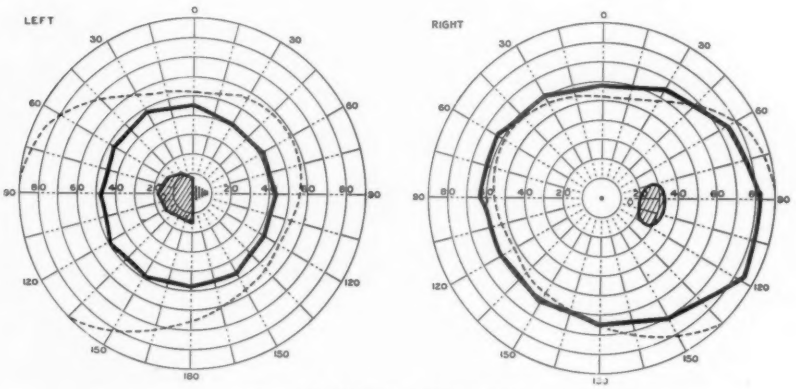

FIG. 16 (Case 9).—Visual fields.

was incurved. Ventriculograms showed a large right ventricle and a small left (15 and 5 c.c. of air respectively). The 3rd ventricle was not filled. There was a large defect at the anterior end of both lateral ventricles, seen in the anteroposterior views to be in the septum pellucidum. A diagnosis of septal cyst was made. On March 24, 1938, a left frontal osteoplastic flap was turned down, the median bone edge on the middle line (G. J.). The left frontal lobe was first elevated and the sphenoidal ridge seen to be free of tumour. The gyrus rectus seemed to be bulky and the chiasma could not easily be exposed. The frontal lobe was readily detached from the falx and an approach made to the cyst through the corpus callosum, after separating the pericallosal vessels from the proposed line of section just behind the rostrum. When this had been divided the thin-walled cyst was at once seen. It contained a quantity of pale yellow fluid. The cyst measured at least 5 cm. in vertical diameter and 4 cm. across. Its walls were paper-thin and easily cut away, thus opening widely into both lateral ventricles. Histologically the tissue removed was reported on as normal septal tissue.

Comment.—The operator was left with the impression that the pathological basis of this case lay in the floor of the septum rather than its walls. It might be that a tumour nubbin was situated in the lamina terminalis, about the anterior commissure or posterior extremity of gyrus rectus. The appearance from below was a little suggestive of this. However, no trace of such a tumour could be seen by inspection of the interior of the large cyst in the septum, and there is no doubt that it was this cyst which was the cause of most of her symptoms and produced the unilateral hydrocephalus by the chance blocking of the left foramen of Monro. Twelve months

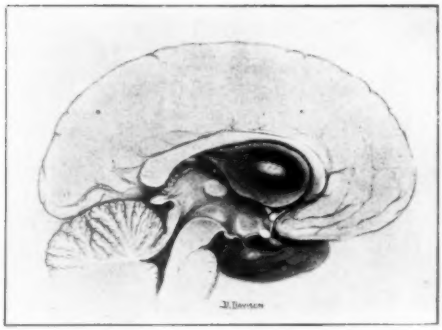

FIG. 17 (Case 9).—Schematic drawing of gliomatous cyst of septum pellucidum.

later this patient is well. The cyst is schematically illustrated in fig. 17, the fluid from its interior contained 53 mgm. albumin.

Case 10.—*Congenital cyst of septum pellucidum.*

Female child, aged 4, with a pituitary stalk (anlage) tumour, with suprasellar calcification. At operation (G. J.) by the transventricular approach the foramen of Monro was found to be blocked by the cyst, but the septum pellucidum was widely distended by a collection of pale yellow fluid. The wall was cut away and the interior of the septum was seen white and non-tumorous. This was clearly a congenital cyst of the septum. Cysts of this kind are not uncommon in hydrocephalus; they are especially to be found in children in whom the normal obliteration of the primitive septal cavity has not firmly taken place. These cysts, as well as those of Verga's ventricle, have been described by Dandy (1931), Van Wagenen and Aird (1934), Wolf and Bamford (1935) and Tönnis (1936), whilst their radiographic appearance has been illustrated by Pendergrass and Hodes (1935). Cells similar to ependymal have been observed lining the septal cysts, but it is not certain that the fluid in the cavity comes from their secretory activities, though it is possible. Van Wagenen and Aird have described other varieties where there are communications between the cavity in the septum and the ventricles, as in a case recently described by Turnbull.

ASTROCYTOMA OF SEPTUM PELLUCIDUM

This case presented a tumour arising from the anterior pillars of the fornix and septum. It protruded into the 3rd ventricle and engaged the foramina of Monro, with consequent obstruction to both lateral ventricles. The tumour was not localized during life because the state of the patient precluded ventriculography.

Case 11.—G. M., aged 18, was admitted to the National Hospital under the care of Dr. F. M. R. Walshe. For a period of two to three months some two years previously he was subject to diplopia; this, however, disappeared and did not recur. Headache accompanied the diplopia, occurred first thing in the morning, was frontal in distribution, and persisted for three or four months. Symptoms then disappeared and he remained perfectly well for a few months. About four months before presentimg himself at hospital he had suffered from pain in the back of the head and also in his left eye; the former pain came on in the morning, was intensified by movement, and was associated occasionally with vomiting; the pain in the eye was of a boring nature, came on at any time of the day and accordingly might, or might not, be concurrent with the occipital pain. For two weeks before admission walking became unsteady. He thought he had been more drowsy during the last two or three weeks.

He was an ill-looking boy who gave a story of prolonged active pulmonary tuberculosis for which hospital and sanatorium treatment had been necessary. Mentally he was rather apathetic, otherwise normal. He had slight swelling of both optic discs, a little more marked on the left associated with striate hæmorrhages. There was a slight weakness of the lower part of the right face. The reflexes were somewhat depressed, probably the result of high intracranial pressure,

and plantar responses were flexor. There was marked spasm of the posterior nuchal muscles. Movement of the head accentuated the occipital pain and caused radiation of the pain down the right arm. His gait was slightly ataxic with apparent difficulty in controlling the right leg and a consequent tendency to lurch to that side.

The history of hydrocephalic disturbance attendant on a prolonged story of tuberculous disease suggested the likelihood of similar disease in the cerebellum. The boy's physical state and the spasm of nuchal musculature were factors in the decision to explore the posterior fossa. At operation (H. J.) the findings were not those envisaged, for a more or less normal cerebellum was

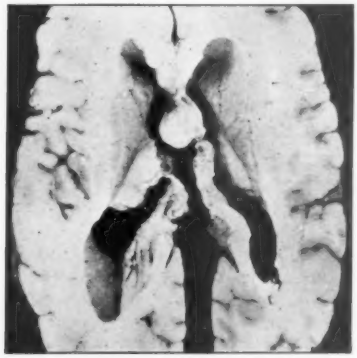

FIG. 18 (Case 11).—Photograph of astrocytoma of septum pellucidum.

encountered, the cisterna magna was distended with cerebrospinal fluid, and no evidence of an obstructive lesion was forthcoming. Following operation he was relieved of headache, ran a normal temperature and pulse, but became completely apathetic and lacking in initiative. He would take his food well, if fed, was doubly incontinent without mental distress, and drowsy. He became finally comatose and died after an interval of four weeks. The question of ventriculographic investigation was considered but his condition was never suitable.

At autopsy a pedunculated mass was found in the position mentioned (*see* fig. 18). This proved to be gliomatous in character, simulating that form of astrocytoma usually found in the cerebellum.

The above case indicates the value of ventriculography in investigation and the essential use of the method with respect to the localization of ventricular neoplasms. There was a period of complete relief from symptoms in the history, but this is by no means limited to tumours in such situations.

An excellent example of an ependymoma of the septum pellucidum showing in the ventriculograms as a symmetrically rounded shadow in the mid-line between the lateral ventricles is figured by Olivecrona and Kessel. No doubt our own Case 11 would have shown an identical appearance. In passing, it might be added that it seems as likely that an ependymoma could arise from congenital rests within the septum as from the cells covering it. A protoplasmic astrocytoma of the septum was described by Bailey in 1929. This was a large tumour, no doubt invasive, for apraxia was present.

INTRAVENTRICULAR ASTROCYTOMAS (ONE CASE)

Besides that just described, there is but one example of a semipedunculated astrocytoma projecting into a lateral ventricle ; there is no doubt that such tumours are very rare. We are indebted to Dr. C. P. Symonds for the history of the case.

Case 12.—*Six years' history of headaches. Diplopia during the worst attacks. Papillœdema. Diagnosis by ventriculography.*

R. H. T., aged 53, was admitted to the National Hospital under Dr. Symonds, having been referred to him by Dr. Brockwell. For six years she had complained of " drilling pains in the head ", mental depression, falling down, and during the past twelve months inability to control her bladder. Her memory was too imperfect for her to be able to give a detailed account of her illness. For twelve months past she had been subject to attacks in which she would suddenly fall, with loss of consciousness. In such an attack the mouth was drawn to the left, both hands twitched, the legs were extended, and she was incontinent of urine. She might be unconscious for fifteen minutes, and she might have as many as eight or ten in a day. For six months she had become more and more confused, with frequent headache and diplopia. Dr. Symonds found papillœdema between 2 and 3 D, slight peripheral contraction of visual fields, coarse tremor in the left hand, all tendon reflexes brisk, both plantars extensor. The left limbs were slightly more spastic than the right, both sides being abnormal. Ventriculograms revealed a small rounded filling defect within the cavity of the right lateral ventricle anteriorly. There was a moderate degree of hydrocephalus on both sides. The diameter of the tumour was *circa* 3 cm.; it lay

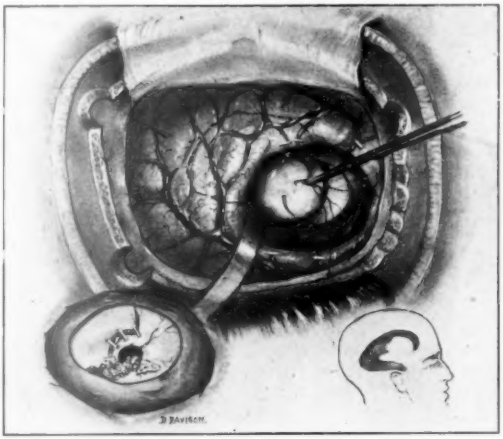

FIG. 19 (Case 12).—Drawing of operative approach to intraventricular astrocytoma. Inset —the foramen of Monro with the choroid plexus as seen after the tumour was removed.

apparently in the floor of the ventricle and might or not obstruct the foramen of Monro. Intraventricular protein was 50 mgm. On July 12, 1935, a small right frontal osteoplastic flap was turned down (G. J.) under local anæsthesia (pre-operative luminal gr. vi and morphia gr. $\frac{1}{6}$). The cortical pattern was normal. A cone 4 cm. in diameter was excised from the right frontal lobe through into the lateral ventricle. The tumour was at once seen glistening white, hard, and avascular (fig. 19). It was sessile but sprang from a base not more than 1·5 cm. in diameter, at the junction of the septum pellucidum with the floor of the ventricle, and just anterior to the foramen of Monro. A medium-sized vein, as well as a few small radicles, ran off the septum on to the tumour. These were coagulated and the tumour freed by cotton pledget dissection. Its removal was facilitated by the insertion of a few silk sutures into the tumour, which was so tough that it held them well. The field after removal was quite bloodless. Convalescence was interfered with by a small cerebrospinal fluid fistula and pyrexia, but in three weeks recovery was complete. Histological examination (Dr. Greenfield) proved the tumour to be a sparse-celled, rather fibrillary astrocytoma. Presumably it sprang from the neuroglia immediately outside the ependymal lining of the ventricle. Dandy, in his monograph, shows one or two photo-

micrographs which resemble closely the appearance of this tumour. He calls them ependymal gliomas, but they look more like astrocytomas.

This is the only case in which a really localized glioma projected into the ventricles to such a degree that it was quite a unique specimen in position and appearance.

Intraventricular Epidermoids

These tumours have so often been described in subhuman species, and only from time to time in man, that there is no doubt the conditions are dissimilar. Only one unquestioned intraventricular epidermoid has been encountered in this series and that is a necropsy finding in a patient not operated upon. Good examples have been recorded by Love and by Tönnis. It is often extremely difficult to say exactly where an epidermoid has originated. We know that epidermoids not infrequently communicate with the lateral ventricles, for ventriculograms of these lesions habitually demonstrate air distributed in a very characteristic fashion in its interstices. None the less such a tumour may prove at operation to be entirely extracerebral and the ventricular communication, presumably usually with the temporal horn or with the 3rd ventricle, not demonstrable. If this type of fistulous opening indicates that the tumour began in the ventricle, then at least one other case ought to have been included. The only undoubted example was the following :—

Case 13.—S. W., female, aged 46, was seen in consultation by one of us (G. J.) in 1937. For twenty years she had had very severe headaches, far beyond anything that could ordinarily be classed as migraine. For the last few years there had been increasing weakness down the left side of the body and for some time she had been hemiplegic. Vision deteriorated first in the right eye, then the left, and now she was blind. There was primary optic atrophy and the usual signs

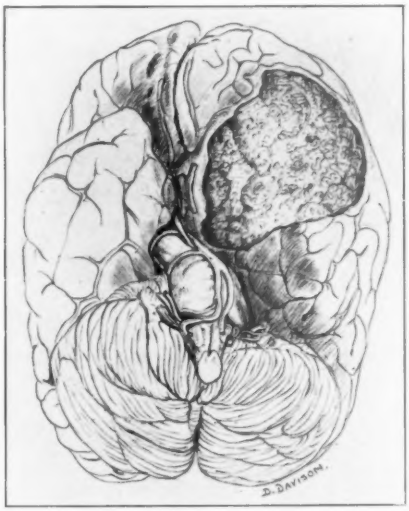

Fig. 20 (Case 13).—Intraventricular epidermoid.

of a hemiplegia with some slight bulging of the right temporal fossa and slight unilateral right exophthalmos. Operation was thought to be inadvisable and a few months later she died. The specimen obtained at necropsy is illustrated in fig. 20. It occupied the right temporal horn of the lateral ventricle which was grossly distended by it. It is probable that by its enlargement the

temporal lobe had directly compressed and dislocated the optic chiasma, so that her blindness was the result not only of chronic papillœdema but of direct pressure as well.

Histologically it was a typical epidermoid. Jefferson believes that these tumours arise in primitive epiblastic rests that have escaped the moderator influence of the other embryonal layers (*see* Rowbotham). In a collected series of 185 cases of embryonic epidermoids (Jefferson and Smalley) there were 27 intraventricular epidermoids, 21 in the fourth and 6 in the lateral ventricles.

Tuberal Cyst of Pituitary Anlage

We have 25 examples of pituitary anlage tumours (tumours of the pituitary duct, generally cystic). The vast majority of these lesions deeply indent the 3rd ventricle behind the optic chiasma and come to occupy the anterior half at least of the 3rd ventricle, rising high enough to obstruct the foramen of Monro. The operative approach of choice to many is transventricular, which can be combined with an anterior infrachiasmal approach as a second stage. The transventricular is indeed the only method which allows of the proper attack on the majority of these cysts for they are not approachable from below until the cyst, which depresses the chiasma, has been removed. In the present communication we intend to report only one of these cases, for it was a primarily intraventricular growth springing apparently from a cell rest in the tuberal floor. There was no extraventricular extension inferiorly and the lesion presented itself both clinically, radiographically, and at operation as a true 3rd ventricle cyst. Histologically it was an unmistakable epithelial anlage cyst of pituitary origin.

Case 14.—J. C. D., male, aged 33, referred by Dr. Dias of Preston, complaining of bad headaches and occasional vomiting during three months. His sister noticed that he was constantly falling asleep and seemed to feel the cold a lot, wanting big fires. He would sit in front of such a fire and sleep most of the day. It was impossible to get any history from the patient for he made no observations whatever except in reply to questions, when he answered monosyllabically. He was a ship's officer and gave an entirely wrong description of his last voyage. During the past week he had been incontinent although quite conscious at the time and seemed quite uninterested in his wet clothes.

On examination, the only positive findings, apart from his mental hebetude and defective memory, were a low-grade papillœdema in both eyes, unequal pupils, the left not reacting to light. The visual fields showed no defect. The blind spots could not be properly charted owing to lack of co-operation. He was admitted to the Manchester Royal Infirmary in July 1936. Ventriculogram showed a rounded filling defect in the anterior end of the 3rd ventricle measuring 3 cm. in height (*see* fig. 21).

A transventricular approach was made 31.7.36. The cortex was 5 cm. thick. The foramen of Monro was at once in view, large and dark-looking owing to its being obstructed by a dark, thin-walled cyst resembling a black grape. In front of the anterior pillar of the fornix the septum lucidum was seen to bulge; evidently the cyst extended far forward as the pneumogram had suggested. The foramen was enlarged by incising the pillar of the fornix forwards, and what appeared to be a very large cyst brought into view. It extended backwards past the foramen for 2 cm. or so. In dissecting out its back end the cyst ruptured and a quantity of yellow fluid with a few spots of shimmering cholestrin escaped. The cyst wall was dissected out as far as possible, but this was very difficult because the wall was so thin that it was continually tearing. In the end it became clear that the risk of removing brain tissue from the 3rd ventricle was considerable. However, most of it had been excised.

The patient made an uninterrupted recovery and remained well for one year, when he returned, having suddenly relapsed. His memory was not good, and he became incontinent again. This had been the outstanding feature. There was no marked return of the hypersomnia, no bulimia or polydipsia. He was once more very slow in answering questions, but he was not so apathetic and unsteady as he had been originally. Visual acuity was normal. There was no sign of a papillœdema. He was readmitted and operated upon, under local anæsthesia, for the second time 19.8.37. On opening the dura the original circular incision of the cortex was easily identified. The hole in the brain had, however, closed without herniation of the ventricular wall through the old opening. The cortex in this area had the characteristic yellow appearance and

rather tough feel of a cerebral scar. The dura was only lightly adherent at one or two points. As soon as the ventricle was opened once more the large foramen of Monro was easily identified. This time it was occupied by a cauliflower-like white papillomatous growth. It could not be drawn through the foramen of Monro, which was much larger than on the previous occasion owing to the incision that had been made into it a year before. It had, however, healed over and looked like a normal, but very large foramen. By careful dissection the tumour was gradually mobilized but every attempt to withdraw it from the 3rd ventricle caused a small portion to break off. The only method of extirpation was with the punch forceps. This was done with little hæmorrhage, the tumour being avascular. By this means an almost complete removal was made but it at no time looked like rocking out and was evidently intimately adherent below to the tuber. Its

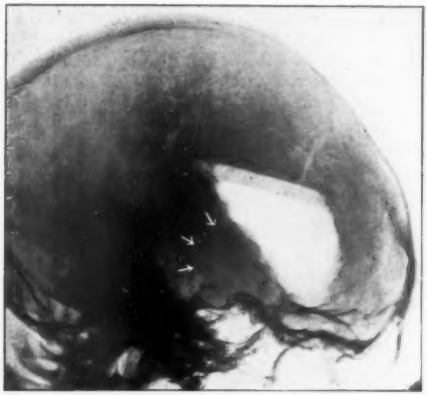

FIG. 21 (Case 14).—Ventriculogram showing filling defect in the floor of the 3rd ventricle anteriorly.

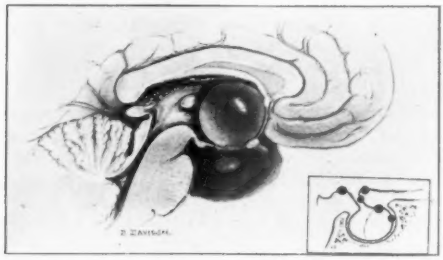

FIG. 22 (Case 14).—Schematic drawing of the pituitary anlage cyst. The inset indicates possible sites of epithelial rests (after Dott).

inferior portion had to be dissected off the neuroglial tissue. This led to a small tear and the escape of fluid from cisterna chiasmaticus. In this way practically the whole of the tumour was excised. On inspection of the tumour bed a perfectly smooth-walled cavity was left ; the opposite foramen of Monro could be clearly seen. The post-operative course was much smoother than might have been expected in view of the presumed damage to tuberal structures. There was a post-operative hyperthermia which yielded to cold sponging. Progress was smooth during the next two weeks, but at the end of that time he suddenly became stuporous and died. Necropsy showed a few tags of tissue left in the floor of the 3rd ventricle with no tumour in the suprasellar region. The cause of death was unexplained, but was no doubt due to a hypothalamic cause.

The interest of this case lies in the absence of any extracerebral extension of this cyst and in the change in the character of the tumour between the first and second operations. The material

removed from the first operation was unmistakably epithelial in appearance. The material from the second operation was of a very much more florid and adamantinomatous type.

Remnants of the anlage of the pars buccalis of the pituitary body may be found at different sites: (1) on the capsule of the gland within the sella, (2) on the stalk, (3) on the pars tuberalis. In the case just described the cyst must have begun from a posterior vestigial remnant of Group 3 (*see* fig. 22). Precisely similar tumours are rare, but a few records in the literature suggest that what the authors have called cystic tumours in the 3rd ventricle have been misinterpreted examples of this type (*see* for instance Draganesco and Sager (1935). Saralegui (1936) and Tönnis (1936) have operated on cysts of the 3rd ventricle to discover later that the tumours were of pituitary anlage origin.

Epiloia

A single, but admirable, example of epiloia was encountered. That intraventricular masses occur in tuberose sclerosis is well known, but it is rare for them to reach such a size as they had done in this case, and rarer still for there to be a definite neoplasm, as was the case here.

Case 15.—*Epiloia. Unilateral fits. Mental retardation. Papillœdema. Retinal phakoma. Ventriculography disclosing intraventricular tumours.*

J. M., aged 7, was admitted to the Neurosurgical Service of the Manchester Royal Infirmary on the advice of Dr. Vipont Brown, on account of fits and severe headaches. She had had left-sided convulsions since the age of 4 months, recurring every two or three days, sometimes many in a day. She never used her left hand and was very backward in walking and talking. She went to school but made little progress. During the last months she had had headaches and occasional vomiting. Examination revealed a shy child who answered questions reluctantly. There was no trace of abnormal cutaneous marking on the face or body. The circumference of the head was 20 in. Both discs showed papillœdema but were difficult to examine owing to lack

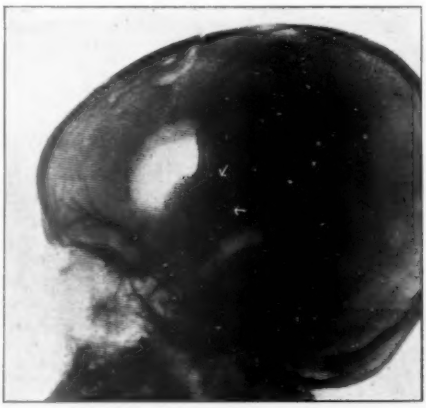

Fig. 23 (Case 15).—Ventriculogram of tuberose projection into anterior horn of left lateral ventricle.

of co-operation. In the left fundus a white patch was seen, a phakoma, below the nerve head (others may have been present). Visual fields were unobtainable. There was a left-sided hemiparesis. X-rays showed a moderately hydrocephalic skull with a small, rather dense calcification the size of a pea, 2 in. above the sella and well to the left of the mid-line. Ventriculograms were made on December 8, 1938, on which Dr. Twining reported "Hydrocephalus with non-filling of the 3rd ventricle and obstruction at the foramen of Monro. A rounded tumour shadow presented into the left lateral ventricle, apparently arising from the floor of the left lateral ventricle. The calcification before observed is embedded in the outer and posterior part of the projecting nubbin" (*see* fig. 23). The fluid from the left ventricle contained 400 mgm. of

protein. The making of the ventriculograms upset the patient so much that nothing further was done for four days, and a short length of sterile ureteric catheter was left to drain the ventricles. The child died eight days later. Necropsy was limited to the head ; the condition found was that characteristic of tuberose sclerosis. There were the usual hard areas of cortical and subcortical sclerosis, but the essential findings were the intraventricular projections. In the right ventricle,

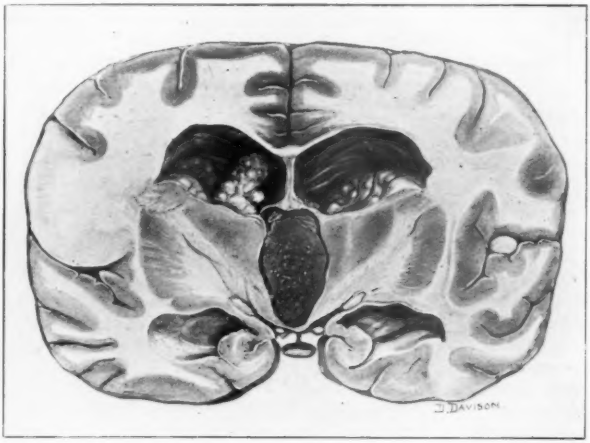

FIG. 24 (Case 15).—Intraventricular tuberose sclerosis with embryonal type of glioma in 3rd ventricle.

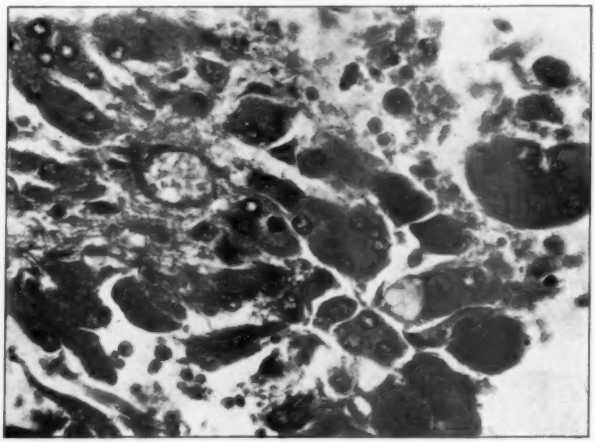

FIG. 25 (Case 15).—Histological section of the 3rd ventricle glioma.

especially over the caudate nucleus, they resembled the more usual " candle droppings ". In the left ventricle over the caudate nucleus were two large intraventricular projections, which proved to be non-neoplastic. The 3rd ventricle was occupied by a quite different tumour, a dark red fleshy mass which filled it like a mould (*see* fig. 24). It was thought that it would most likely prove to be an ependymoma, but Dr. Greenfield describes it as an embryonal tumour (fig. 25)

similar to those sometimes encountered within the central neuraxis in multiple neurofibromatosis.

The fits in this case had developed shortly after vaccination, and the case was thought originally to be one of vaccinial encephalitis. It is a good example of the difficulties attending the diagnosis of epiloia in the absence of cutaneous manifestations (*see* Brushfield and Whyatt (1926), Critchley and Earl (1932), Russell Brain and Greenfield (1937)). The presence of the so-called " Bourneville phakomata " is the most useful clue. The intraventricular nodules of tuberose sclerosis have been demonstrated by encephalography in one other case (Berkwitz and Rigler (1935)). Their case was a child 2 years and 1 month old with fits and mental retardation. The pneumograms show very clearly the large irregular projections of tuberose masses into the ventricles. Another example, A. A. McConnell's, of 3rd ventricle glioma in this disease, was referred to as privately communicated to Critchley and Earl for their comprehensive paper on epiloia (1932). The tumours that have been rarely found in epiloia have generally been primitive spongioblastomas (*see* Lhermitte, Heuyer, and Vogt (1935) and Cook and Meyer (1935)), though Globus, Strauss, and Selinsky (1932) in their report of 11 tumours in this condition call them neurospongioblastomas.

The Ependymomas

It comes as something of a surprise that there should be so few ependymomas in this collection. This is the more striking because Dandy's monographs contain several striking examples of gliomas that he calls ependymal. Our experience has been different, for we have found that when the ependymoma forms a massive tumour its bulk is often buried in the hemisphere, and that although it abuts on the ventricle and invaginates it, scarcely does it do so more than other types of gliomas. When, on the other hand, it makes its appearance as a true intraventricular tumour, it is usually more malignant and forms a plaque-like tumour liable to seed over the ventricular surfaces, to drift into recesses and obliterate them by local proliferation. In three cases in this series an ependymoma overlay the entrance of the iter, which it blocked, causing an outspoken hydrocephalus. In two of these there was a filling defect in the ventriculograms suggestive of pinealoma, in the third the tumour did not cause any recognizable salience in the pneumograms. They will not be further described because they will be better dealt with in a separate paper. It might be pure chance that no pedunculated or semi-sessile ependymoma has presented itself in the experience of either of the present writers. Dandy's magnificent pictures, elaborated from operation sketches, are accompanied by histological sections named " ependymal gliomas ". It is difficult to be certain of the structure of these tumours from the photomicrographs published ; one looks like an astrocytoma, others like astroblastomas. One can assume only too readily that an intraventricular tumour has arisen from the lining cells, but there is no certainty of the correctness of such a deduction. As we have already stated, the commoner massive ependymomas seem to abut on the ventricles and to bulge into them, but with so broad a base that they are as much extra- as intraventricular tumours. Indeed in the largest of them that we have had the ventricle was only opened in the last stages of removal, the tumour having been dissected from the surrounding white matter in which it was completely buried, save for an area of a centimetre or two on its deepest surface, where it reached the ventricle. Ependymomas in the 3rd ventricle, besides our own, have been reported by Dandy, Allen and Lovell, Kessel and Olivecrona, Vonderahe and Abrams, Fincher, and Tönnis.

The Autonomic Disturbances Accompanying Intraventricular Tumours

A syndrome of the 3rd ventricle was postulated by Weisenberg as long ago as 1910, but even before that its lesions had been thought to call for special comment (*see* Mott, 1900, Hinds Howell, 1910). At those dates little was known of the central representation of autonomic mechanisms (*see* Sheehan's historical review) and little useful survives of the original syndrome save certain eye signs and hypersomnia.

Good accounts of the modern physiology, and of the clinical, signs have been given by Beattie, Riddoch, and Dott (1938).

The occupation of the 3rd ventricle by some of the tumours in this series would lead us to expect some noteworthy examples of disturbances of the autonomic nervous system. Nothing approaching Penfield's example of diencephalic epilepsy nor of Russell's and Byrom's rather similar but more chronic case happens to have been encountered, and the signs that we have come to regard as hypothalamic, though sometimes present, were not outspoken and rarely recognizable as leading signs. Not recognizable, that is, in the sense in which we understand the localizing meaning of a local epileptic fit. Although the sites of the cell groups probably interested are well enough known, their relationships to individual functions are not yet agreed upon. It must be admitted that of all the possible signs—diabetes insipidus, disturbances of temperature, of respiration, of cardiac rhythm, of gastric motility and secretion, of blood-pressure, of sleep, of appetite, and of fat storage—the exact site of the lesion can be foretold only as concerns diabetes insipidus (nucleus supra-opticus and supra-optico-hypophysial tract). We need all the evidence that we can get to establish more certainly the control of the other metabolic functions, the more probable sites of which, to be sure, are already conjecturable. Have we, in actuality, any great reason to expect autonomic disorders from the purer types of intraventricular tumour, which at most merely indent the ventricular walls but do not invade them ? We should say no, the more so because the relevant cell groups are commonly not so nearly subependymal as is implied by such a commonly used, but loose, term as " centres in the walls of the 3rd ventricle ". Further, the list of tuberal or hypothalamic physiological deficiencies just given is a very mixed one in the sense that some practically never occur as leading symptoms or signs, that only a few can be chronic and so are only seen in the most acute forms of hypothalamic disaster. It seems to us that the disturbances of function most commonly seen in true intraventricular tumours are due to hydrocephalic dilatation of the 3rd ventricle and to impairment of blood supply to the neighbourhood. They do not differ very greatly in type or frequency from those seen in cases of ventricular distension from other causes (e.g stricture of the iter, benign cerebellar tumours, and meningeal hydrocephalus), where the most outspoken evidences are apt to follow a sudden lowering of pressure by operation and to appear in an acute form. The results of sudden flooding with blood of the previously anæmic areas is similar to that seen after the too-sudden decompression of hydronephrotic kidneys. Punctate hæmorrhages may stud and star the ventricular walls. In the most perfect of intraventricular tumours, the colloid cysts, the lesions lie just below the roof of the 3rd ventricle, whilst most of the relevant autonomic nuclei are chiefly grouped around the ventral portion and could only be affected by the distant effects of cerebrospinal fluid pressure, either on the vascular irrigation of cell groups, or less probably by exerting tension on tracts.

The literature of the colloid cysts supports in the main the views just expressed, and, though there are exceptions, the explanation of them depends on variants of possibilities mentioned just now. Of the 28 cases collected by Zimmerman and German, hypersomnia was present in three, frequent yawning in another, polyuria in one, pupillary changes in five. In Stookey's analysis of 39 examples of colloid cysts hypersomnia was present in 39%, diabetes insipidus in 10%, hyperthermia in 10%, adiposity in 3%. In contrast, in the case recorded by Byrom and Dorothy Russell the autonomic signs were remarkable (intense hunger, extreme drowsiness lasting several days at a time, sugar and acetone in the urine, subnormal temperature), but here the cyst seemed to have been present for twenty years. The great chronicity of the lesion, the intermittent nature of the cerebrospinal fluid obstruction, must have given the tumour unusual opportunities for the production of vegetative disturbances, f not by its own local pressure then by varying tension on the vascular supply to nearby cell-clusters. Our own cases can be tabulated as follows :—

TABLE OF SPECIAL SIGNS

Case 1.—Lateral ventricle meningioma	Fits. No tuberal signs. Periodic weakness of legs.
Case 2.—Meningioma of 3rd ventricle	Hypersomnia.
Case 3.—Lateral ventricle meningioma	No tuberal signs.
Case 4.—Colloid cyst	No tuberal signs. Posture relieved headache.
Case 5.—Colloid cyst	Hypersomnia. Periodic weakness of legs.
Case 6.—Colloid cyst	Periodic weakness of legs.
Case 7.—3rd ventricle dermoid. ..	Periodic weakness of legs. No tuberal signs. Posture relieved headache.
Case 8.—Papilloma of choroid plexus	No tuberal signs.
Case 9.—Septal cyst	No tuberal signs.
Case 10.—Septal cyst	Tuberal signs probably present.
Case 11.—Septal astrocytoma	No tuberal signs.
Case 12.—Intraventricular astrocytoma	No tuberal signs.
Case 13.—Intraventricular epidermoid	No tuberal signs.
Case 14.—Tuberal cyst	Marked tuberal signs. Hypersomnia and polyuria. Hyperthermia.
Case 15.—Epiloia	No clear tuberal signs.

Even with regard to such general signs as headache and its relation to posture, too much can be made of these points as having a diagnostic meaning. Headache causing postures, and the converse of the adoption of certain postures to avoid it, are a common feature of posterior fossa tumours. The inadequacy of evidence irrefutable to hostile criticism is well seen on reference to Stookey's Table IV (influence of posture on headache) where the evidence of 9 cases out of 23 is put forward. It is not very convincing. We believe, however, that there is something in the point, but it has not been properly expressed. It is the influence of a special posture either of the head or the whole body in relieving sudden intense headache of an intermittent type. It is only really significant in those persons who are entirely well in between their paroxysmal hypertensive attacks, and then find relief by some alteration in the position of the head. This is different from the postural amelioration of the more continuously present headache of other kinds of tumour. Hypersomnia needs qualifications of much the same order. It is not always easy to be certain in patients with increased pressure that it has a local significance and that it is not mere evidence of pressure on neural mechanisms in a wider sense. It is the fact that so-called hypersomnia may not be a strictly accurate account of the patient's state ; it requires very careful observation and description before we can accept it as having been present beyond any doubt. Probably hypersomnia always has some local significance in patients short of stupor (and maybe even in them also), but it cannot be used as a crisp differential sign because extraventricular parathalamic lesions show it as well or better. In Case 5 (colloid cyst) above there is little doubt that true hypersomnia was present. There is no mistaking, on the contrary, what we mean when we speak of the other autonomic activities. But if one wishes to adduce evidence of autonomic disturbances of the major kind one must seek amongst the pituitary anlage group, and especially amongst the invasive, malignant tumours (especially the secondary carcinomas) that may invade the hypothalamus, or amongst the post-operative disturbances. It is quite certain in our experience that disturbances of water metabolism, for instance, are much commoner with lesions that actually cut into hypothalamic and tuberal structures and that mere pressure by a benign lesion does not readily release them. Dott's experiences with the pituitary stalk tumours and Max Peet's and Edgar Kahn's support our own observations.

As for the post-operative upsets, the small and often unimportant capillary hæmorrhages and local œdemas that follow interventions in the neighbourhood of the third ventricle may cause autonomic phenomena to appear when they were not there before. In Case 12, for example, there was high fever for eight days after operation, but the reassuring thing was that the patient felt very well and ate very

well in spite of it. (There is always the chance that pyrexia after an intraventricular operation may indicate infection.) In Case 2 of Zimmerman and German, who died after a first-stage exploration for a colloid cyst, the patient before death had crises of sweating, elevated blood-pressure, slow pulse with extrasystoles, cyanosis, and irregular respiration. Mild disturbances of a same nature may be read of in the reports of other surgeons, and there is the well-known case of Penfield, of diencephalic epilepsy where all these symptoms and signs in the post-operative course are admirably recorded. As for eye-signs and limb weakness, the observation in Case 6 of the colloid cysts of the depression of the pineal, is suggestive (fig. 11, p. 69). It is probable that this indicates a crowding into the hiatus tentorii, and from a drift like this into the relatively low-pressure area of the posterior fossa secondary neurological signs are known to occur commonly. This subject has recently been discussed by one of us. The case reported by Stern and Moore (1938) where a colloid cyst of the 3rd ventricle caused a homonymous hemianopia by strangulation of the posterior cerebral artery on the tentorial edge further emphasizes this point. The hydrocephalus alone may either depress the tectal part of the mid-brain by dilatation of the 3rd ventricle backwards above it or alternatively compress it by general dilatation of the lateral ventricles. The latter would be more likely to press the pineal shadow downwards than the former. Depression of the pineal shadow in hydrocephalus caused by colloid cysts was noted by Davidoff and Dyke in two cases out of four in which the pineal was visible.

We may conclude therefore with the observation that hypothalamic disturbances in true intraventricular tumours are the result of alterations in tension in a dilated 3rd ventricle and to the disturbances of blood supply in neighbouring structures. We conclude also that there is nothing in them specifically informative as to the exact nature of the lesion, that they are often minimal because the benign nature of most of the true tumours within the ventricles tends to a slow, sometimes an intermittent, evolution, so that compensatory mechanisms can negative an expected result. We have encountered tuberal signs more often in paraventricular and especially in invasive lesions.

Cerebrospinal Fluid in Intraventricular Tumours

As a rule the fluid in hydrocephalic ventricles has all the attributes of the normal. If anything the protein content tends to be low. It would be expected that when a tumour is located in a ventricle it will add its metabolites to the fluid. Furthermore, when one foramen of Monro is blocked, there should be a considerable difference in the protein from the two sides. Basically the increase of albumin, which is the most easily estimated and most usual measure of fluid alteration, depends on the vascularity of the lesion. These facts are well illustrated by the estimation of the fluids from the present series. The highest count was in the case with a papilloma of the choroid plexus where the albumin in the xanthochromic ventricular fluid measured 1,800 mgm.% (cp. Van Wagenen's case—2,062 mgm.). In the epiloia with a vascular tumour in the 3rd ventricle the figure was 400 mgm. In one of the meningioma cases the fluid contained 180 mgm. in the left ventricle (where the tumour lay), and only 50 mgm. in the other. In another case not reported here (G. F. Rowbotham, personal communication) the fluid from one ventricle containing an ependymoma clotted on cooling, that from the other contained 600 mgm. of protein. As against these figures the intraventricular fluid in one of the astrocytoma cases was no more than 50 mgm., and in one of the colloid cysts 35 mgm. These increases of cerebrospinal fluid albumin are reflected in the lumbar fluid, for we cannot imagine a ventricle to be sealed off to such an extent that nothing escapes from it at all, though this happened to one occipital horn in Case 3. But a raised protein in the fluid withdrawn by lumbar puncture has no special localizing meaning, it indicates that a tumour has access to the subarachnoid or ventricular spaces, and

that is often useful information. A high protein on ventricular puncture, on the other hand, has a more recognizable message, but it is not often that we have an opportunity to make use of it because the fluid is usually withdrawn only in the course of the operation on the tumour. It is, therefore, not of such practical service as it would otherwise be. In an analysis of ventricular fluids by C. C. Hare (1935) high proteins were encountered, especially in glioblastomas and medulloblastomas. In the former the lesion often extends so deeply that it involves the ventricular wall; in the latter the tumour has free access to the fluid quite apart from the possibility that it has seeded into the ventricles. We must conclude that a high ventricular protein may accompany a benign tumour in the ventricle, but that it is just as likely to indicate that a malignant tumour of the hemisphere or cerebellum is washed by the cerebrospinal fluid.

Ventriculographic Diagnosis and Pseudoventricular Tumours

Intraventricular tumours are most likely to be found in those who have pressure signs but no localizing signs, the kind of picture so often given by serous meningitis. Although it may be possible to suspect the presence of an intraventricular tumour by the more ordinary clinical methods of deduction, the final diagnosis is essentially radiological. Without this aid it would usually be impossible to know with sufficient certainty whether the bedside impression was right and to plan the correct operative approach. The prospects of success are as good as they were in Dandy's first ventriculogram on October 6, 1918. In that now historic case an intraventricular meningioma was visualized and successfully removed.

Lateral ventricles.—Since the diagnosis depends so much on the correct interpretation of the ventriculograms a few words should be added on this subject. In all cases the ventricles are above normal size, though sometimes (as in the choroid plexus tumour) the hydrocephalus is unilateral, or if not strictly unilateral, one side is distinctly larger than the other. It may be doubted whether an entirely one-sided hydrocephalus can ever occur. Either the process which causes it affects as well the contralateral side in some degree, or else that side is altered by the general effects of distortion induced by the ipsilateral ventricular enlargement. As a generalization, one has as a ground-plan in intraventricular tumours a hydrocephalic ventricular system and into some part of it the tumour which obstructs the circulation of the cerebrospinal fluid makes a salience, appearing on the film as a filling defect. Examples have been given in the previous sections of this paper. Difficulties may arise as to the meaning of these defects, and it is sometimes not easy for the observer pre-operatively to be sure that a tumour is truly ventricular and is not bulging into it whilst its main mass lies outside it. It may be the case that the final topographical, no less than the histological, diagnosis must await exploration. An incision through the cortex may be necessary before the surgeon can tell which he will encounter first, tumour or ventricle. This brings us to the matter of the pseudoventricular tumour.

The defect exhibited by the first intraventricular meningioma can be paralleled by another example where a large ependymomatous cyst lying chiefly outside the ventricle projected much of its bulk into the cavity of the lateral ventricle (*see* fig. 26). The case was one of a female aged 15 with a few weeks' history of headache and vomiting, a left inferior quadrantic homonymous hemianopia and bilateral papillœdema. This cyst was opened into the temporal horn and trigone of the lateral ventricle by wide removal of its medial wall (G. J.) with survival of the patient in excellent health three years later.

On other occasions tumours of the basal ganglia have thrown shadows very suggestive of a localized intraventricular lesion. An admirable example is figured in figs. 27 and 28. The tumour is an astrocytoma of the optic thalamus and was found at post-mortem at the Manchester Royal Infirmary on a 15-year-old boy with a

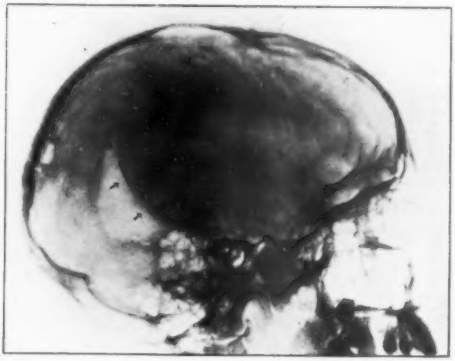

FIG. 26.—Ventriculogram of hemispheral cyst indenting lateral ventricle. For comparison with fig. 4.

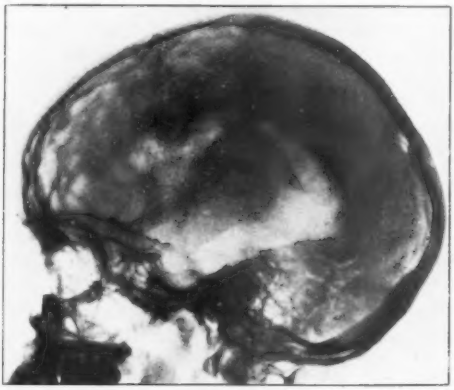

FIG. 27.—Ventriculogram of pseudo-intraventricular tumour—actually astrocytoma of right optic thalamus.

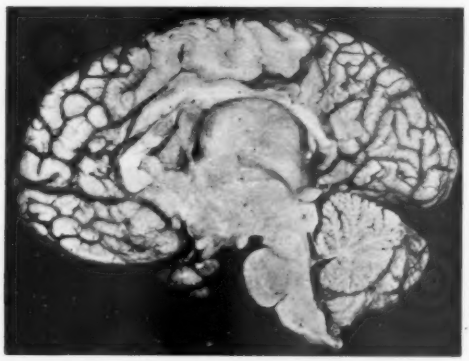

FIG. 28.—Specimen illustrated in fig. 27.

history of six months' dizziness, vomiting, and headache, with unsteadiness on the feet and slight bilateral ptosis but no pyramidal signs. No operation was done for the nature of the lesion was suspected. It seems to us to be the fact that local thalamic tumours even more than those of the caudate nucleus produce ambiguous ventriculographic pictures; the problem is usually solved by close correlation of the history and signs with the X-ray evidence. Thalamic tumours undoubtedly produce internal hydrocephalus by narrowing the cleft of the 3rd ventricle, especially at its posterior end. Into this they bulge as a unilateral mass. Case 1 (a secondary carcinoma occupying the right optic thalamus), of the first thorotrast ventriculograms to be published in this country (Twining and Rowbotham) illustrated this point well. The clinician will be very suspicious of any shadow which cannot be separated from that of the optic thalamus, which normally produces so distinctive a feature of both lateral and frontal radiograms (in the latter particularly when the ventricles are enlarged) and especially in the Towne and reversed Towne projections.

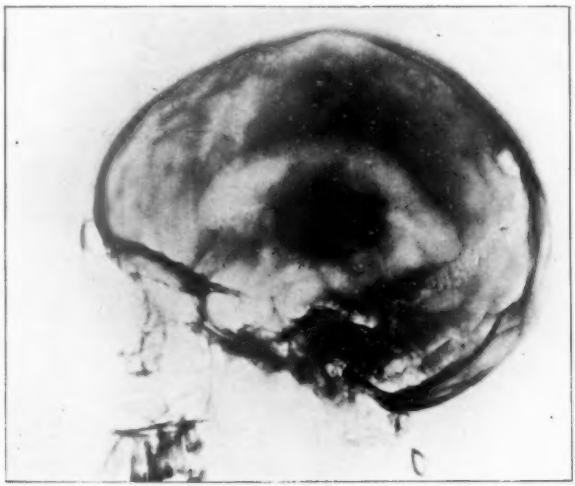

FIG. 29.—Filling defect of back end of 3rd ventricle caused by astrocytoma of optic thalamus.

The subject could be illustrated much more fully, but it would lengthen tediously this discussion. The appearances of an intraventricular tumour have not only been demonstrated in these pages but, with the reservations just given, can be imagined almost by definition alone.

3rd ventricle.—We have assumed that the reader is familiar with the appearances of colloid cysts and others in this ventricle, so that filling defects, whether of the anterior or posterior end, will be left on one side. They have received, and are receiving still, considerable attention in the radiological journals (*see* Lysholm, Twining, Johnson and List, David, Davidoff and Dyke).

One further case of pseudoventricular tumour is illustrated in fig. 29. This again is a glioma of the optic thalamus (spongioblastoma multiforme) producing a cut-off of the back of the 3rd ventricle, and simulating a pineal tumour. Figs. 27–29 make it clear that great care is needed in accepting certain appearances as evidence of a probably enucleable lesion.

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Radiotherapy of Intracranial Tumours with Special Reference to Treatment of Pituitary Tumours

By A. ORLEY, M.D., F.F.R., D.M.R.E.

CEREBRAL neoplasms, including tumours of the hypophysis, form about 2% of all cases of cancer.

The relative proportions of the main different types of cerebral neoplasm are approximately as follows :—

Gliomas	43%
Pituitary adenomas	19%
Rathke's pouch tumours ..	5%
Meningiomas	12%
Acoustic tumours	9%

Our knowledge of radiosensitivity of the different types of glioma and of what should be considered an adequate tumour dose has been greatly enriched during the last few years, mainly thanks to the research work of neurosurgeons, radiologists, and pathologists in the United States of America. We also know now more or less exactly the single dose of the X-rays which the brain can stand without subsequent ill-effects.

Experiments have definitely proved that the adult brain is one of the most radio-resistant tissues of the body. Large doses of X-rays, however, such as used in the

treatment of glioma, may produce microscopic vascular lesions, which usually do not produce clinical symptoms. On the other hand histological examination of the brain before and after irradiation has shown which of the gliomas are radiosensitive, the degree of their radiosensitiveness, and the effect of doses of different strengths. Here is a table of the relative proportions of the most important types of glioma. The different types are arranged in order of their radiosensitiveness :—

Type of tumour	Frequency of occurrence
(1) Medulloblastoma	13%
(2) Ependymoma	3%
(3) Astrocytoma	37%
(4) Glioblastoma multiforme ..	30%
(5) Oligodendroglioma	4% (radioresistant)

Both clinical and pathological studies have proved that the most radiosensitive gliomas are the medulloblastomas, particularly the cerebellar medulloblastomas in children. In view, however, of the tendency of these tumours to form implantation-metastases along the subarachnoid system, the whole of the cerebrospinal axis should be irradiated. The results of occipital decompression to relieve hydrocephalus, followed by radiotherapy, are as good if not better than the results of removal of the growth.

Next in order of radiosensitiveness come the ependymomas. The tumour dose should be as large as compatible with skin tolerance and is in the neighbourhood of 4,000 r.

The astrocytomas, which form the largest group of cerebral gliomas, are relatively benign tumours, but are radiosensitive to a certain extent. Although the primary tumours may appear benign, the not-infrequent recurrences are often of a more malignant nature. Post-operative radiotherapy seems to counteract the tendency towards malignant recurrences.

The glioblastoma multiforme, this highly malignant glioma which no neurosurgeon would touch if he could help it, usually clinically benefits by the radiation, at least for a time. Thanks to irradiation the average post-operative survival has increased from about nine months to two years. The treatment must be intense and the intervals between successive courses of treatment short.

Blood-vessel tumours, which represent about 2% of all intracranial tumours, can be divided into angiomatous malformations and hæmangioblastomas, which are true tumours. Irradiation of inoperable tumours and post-operative irradiation following the removal of an hæmangioblastoma is definitely useful. Vascular malformations should be treated by radiation rather than by excision. Even an audible bruit betraying an arteriovenous communication may disappear after irradiation. The radiation damages the vascular endothelium and causes thrombosis and obliteration of the vessels.

Of the remaining types of glioma investigated the oligodendrogliomas, which are relatively benign tumours, are definitely radioresistant.

In a large number of cases radiotherapy is used in conjunction with a decompression or removal of the tumour and it is very difficult to assess exactly the degree of usefulness of the radiation. I should like, however, to quote two illustrative cases which were treated by radiation only. One, a patient of Dr. Yealland, a man aged 42, with a history of cerebral tumour dating from 1934. When he first came to the hospital in 1937 he complained of continual headache, which kept him awake at night, and of inability to walk owing to numbness and spasticity of left arm and leg. A radiograph of the skull showed an extensive destruction of the sella turcica, in this case the result of a long-standing increase of the intracranial pressure. A tumour of right pre-Rolandic area was diagnosed, and as the patient refused any surgical interference, it was decided to treat him by radiation. After the first course of treatment the headaches and paralysis disappeared and he was able to resume his work at the

Woolwich Arsenal, where he has been working ever since, often as long as eleven hours a day. He has had several courses of X-ray treatment as an out-patient during the last two years and is having a course of treatment at the moment.

The other case, a patient of Dr. Worster-Drought, was a man aged 50, suffering from an intrapontine tumour. He was brought into my consulting room on a stretcher, paralysed and semiconscious. At the end of the course of X-ray treatment he was able to walk almost unaided the flight of stairs leading into my consulting room, and a month after the end of the treatment he was able to drive a car and mow the lawn.

In the greatest majority of cases, however, the growth sooner or later recurs. It can be kept in check by further courses of treatment, but a time necessarily arrives when the scalp is unable to stand radiation any longer.

In such cases the direct irradiation of the tumour or tumour-bed in cases of removable tumour, may still be attempted. The tumour is exposed, the osteoplastic flap turned down, the area to be treated is covered with sterile cellophane, the scalp is covered with several layers of sterile thin lead foil, and the exposed area is given a dose of 3,000 to 6,000 r. Direct irradiation of the tumour or of the tumour bed with soft unfiltered radiation has recently been suggested as an alternative to the usual deep therapy through the closed skull.

I have not included meningiomas in this review because these tumours are definitely radioresistant, although various workers have reported favourable results from radiotherapy of meningiomas. I think that the good results are due to the secondary action of the radiation on the choroid plexuses and not to a direct effect on the tumour itself. Meningiomas are very slowly growing tumours and for this reason the cranial cavity gradually adapts itself to the increased intracranial pressure up to a point. A moment, however, arrives when the adaptation mechanism breaks down and the symptoms of tumour become acute. The radiation inhibits the choroid secretion and as a result less cerebrospinal fluid is produced. The intracranial tension slightly decreases, the circulation and consequently the absorption of the cerebrospinal fluid in the subarachnoid spaces improves. The improvement, however, lasts only until the adaptation mechanism irreparably breaks down again. In the meantime valuable time may have been lost and the operative risk become much greater.

The craniopharyngiomas form a kind of logical link between the gliomas and pituitary adenomas. The operative mortality for these tumours is rather high. One of the dangers of the radical operation in the case of moderately sized tumours is interference with the thermo-regulating centre situated in the wall of the 3rd ventricle. This may result in a fatal hyperpyrexia. In view of this it has recently been suggested that the smaller tumours should be treated on more conservative lines. Only part of the cystic wall of the tumour (in case of cystic tumours) should be removed, and the operation should be followed by a course of radiotherapy, which prevents the re-accumulation of fluid in the cyst. This method of treatment seems to give better results than the more radical operation.

What are the ultimate results of radiotherapy in cases of glioma? Here is a statistical survey by Cairns of post-operative survival of glioma operated at Cushing's Clinic in 1926–27 :—

Type	Total	Dead						Alive 7-9 year after operation
		0-1	1-2	2-3	3-4	4-5	7-8	9-10	
Glioblastoma-multiforme	8	6	2						
Medulloblastoma—									
Cerebellar	5	2	3						
Cerebral	2				1	1			
Astrocytoma—									
Cerebellar	4	1							3
Cerebral	15	1	7	3		1	1	1	1
Total	34	10	12	3	1	2	1	1	4

Alive after five years—6 cases = 17%.

Of a series of 27 cases of cerebral tumour treated by Schinz in Zurich during 1919–1935, 16% were alive and well after five years.

There is therefore little difference between the ultimate results of the two methods of treatment, except for the bedraggled appearance of the patients who have been exposed to repeated intensive courses of radiotherapy. There is, however, no doubt that the final results in operable cases could be considerably improved by a combination of surgery and radiotherapy.

Let us turn to pituitary adenomas. They are divided into several histological types :—

Chromophobe adenoma	68%
Chromophil adenoma with acromegaly or gigantism	23%
Mixed adenoma	13%
Rapidly growing or malignant adenoma	2%

If there is practically unanimity between neurosurgeons and radiologists with regard to the respective merits of surgery and radiotherapy in tumours of the brain and meninges, no such unanimity exists in connexion with pituitary tumours. As recently as 1935 Cairns, in a paper on pituitary adenoma published in the *Lancet*, states that there is no evidence that radiotherapy is of any value in chromophobe adenoma, but he concedes that some acidophile adenomas are radiosensitive. This statement, while partly true, is somewhat misleading. We have no evidence that the radiation acts directly on the chromophobe cells of the adenoma, but there is both clinical and pathological evidence that in a large number of cases the adenoma shrinks following radiotherapy, possibly as a result of an obliteration of the blood-vessels.

Here is a summary of results of radiotherapy in seven cases of chromophobe adenoma as reported by Schnitker, Cutler, Bailey and Vaughan in an analysis of 81 cases of chromophobe adenoma treated by either radiation alone, or by operation alone, or by a combination of radiotherapy and surgery :—

	Visual improvement (100 % being taken as full normal vision).	
Case 1	90%	
Case 2	90%	
Case 3	50%	
Case 4	25%	Subsequent operation.
Case 5	25%	
Case 6	100%	
Case 7	15%	

Average visual improvement (in 6 cases) 61%

Statistics based on larger series of cases, however, show less favourable results.

In deciding between operation and radiotherapy we have to consider four factors : (1) operative mortality, (2) chances of five years' survival, (3) stage of the disease, (4) chances of improvement of vision.

(1) The operative mortality in pituitary adenoma varies from one clinic to another. In Cushing's series the operative mortality for chromophobe adenoma was 3·8% and 10% for the eosinophile adenoma. In a recent article published in the *British Medical Journal*, Jefferson mentions 15 consecutive operations for pituitary adenoma without a single fatality. This is a remarkable record of which any neurosurgical clinic could be justly proud. But, on the other hand, some of the neurosurgical clinics report an appallingly high mortality of 30%. It would be equally fallacious to accept this as typical as it would the latest figures of Jefferson. In computing the results of the different clinics we arrive at a somewhat arbitrary figure of an average mortality of about 10%. The operative risks are therefore considerable, while the mortality from radiotherapy is practically nil.

(2) In the previously cited analysis of the results of operations for cranial tumour in the year 1926–27 carried out at Cushing's Clinic, Cairns reports 65% of the patients operated for pituitary adenoma surviving seven to nine years. In reviewing the results of radiotherapy in 5,000 cases of cancer Schinz, in a paper published in the last October issue of *Strahlentherapie* states that 60% of the patients treated by radiation for pituitary tumour were alive and well after five years. From this point of view there is therefore little to choose between operation and radiation.

(3) The evolution of pituitary tumours can be divided into three stages: the endocrine, ocular, and tumoral.

There is probably complete agreement as to the treatment of the endocrine phase. The treatment should be by radiation. But no hard and fast rules can be laid down, and should there be an encroachment on the visual fields in spite of repeated courses of radiation, the patient should be handed over to the surgeon. There is also complete agreement about the course of treatment of the third or tumoral stage. Here it is no more a question of saving vision, but of saving life, and the treatment should be surgical in spite of increased operative risks. The choice of the best treatment for the second, ocular stage, brings us to factor

(4) The question of restitution or preservation of eyesight. In the following table I have tabulated the results of surgery as given by Cushing and the results of radiotherapy in a series of 20 cases treated by radiation only by Hare and Dyke.

	Cushing's operative series	Hare and Dyke's irradiation series
Restoration of vision	21%	10%
Improvement of vision	42%	20%
Vision unchanged		40%
Vision decreased (operation refused)		30%
General symptoms improved ..		75%
Mortality	5·7%	0

It is difficult to reconcile the post-irradiation results as shown here with those already quoted from the paper by Schnitker, Cutler, Bailey and Vaughan. The last, however, as already mentioned, are not typical, being based on a too-small number of cases. From a careful perusal of the literature one gains the impression that chances of improvement of vision are greater after operation than after treatment by radiation.

This is due to several factors. In the first place about 15% of all pituitary adenomas are cystic and X-rays have no effect on such tumours. Then, a certain proportion of solid adenomas are definitely radioresistant.

We can therefore summarize the position as follows: operative mortality about 10%, no mortality due to radiotherapy. Chances of five years' survival approximately equal for either operation or radiotherapy. Chances of improvement of eyesight better after operation than after radiotherapy.

In view of this the proper policy in all cases of pituitary adenoma, except in those cases which have reached the tumoral phase or where there is the danger of a rapidly progressive loss of eyesight, the patients should be given the chance of radiotherapy. The visual fields, however, must be controlled at frequent intervals and any non-transitory deterioration of eyesight should call for an immediate operation. Transitory visual deterioration, lasting only a few days but followed by an improvement of the eyesight, may occur as a post-irradiative reaction.

The patients must be kept under proper ophthalmological control for a considerable time after the irradiation. It has been our practice to repeat once or twice the course of treatment. Even repeated courses of irradiation do not in any way prejudice the results of a subsequent operation should such an operation become necessary.

Good results from radiotherapy have also been reported in dystrophia adiposo-genitalis. Thus Küpferle and Szily have treated 16 cases of dystrophia adiposo-genitalis with the following results :—

Improvement of eyesight in 13 cases ..	80%
Relief of dystrophy in 6 cases	37%
Genital function not relieved in a single case.	

Recurrences after operation for pituitary adenoma occur in about 10% of cases. It is mainly for this reason that post-operative radiotherapy has been advocated in all cases of pituitary adenoma. Post-operative radiotherapy seems also to improve the prognosis as regards eyesight, as can be seen from the following table :—

CHROMOPHOBE ADENOMA. IMPROVEMENT AFTER TREATMENT.

(Schnitker, Cutler, Bailey, and Vaughan.)

	Operation only	Operation plus irradiation
Number of cases	33	42
Average improvement of visual acuity* ..	⅞	⅞
Average improvement of visual fields ..	24%	29%
Duration of visual improvement ..	3 years	4 years

* Percentage in comparison to condition on admission, not to normal.

In the limited time at my disposal I have been able to give only a very cursory review of the subject. I hope, however, that the discussion will elucidate a number of points only briefly touched in this review.

Summary.—Most of the gliomas are radiosensitive, but the degree of radiosensitivity varies with the histological type in the descending order : medulloblastoma, ependymoma, astrocytoma, and glioblastoma multiforme. The oligodendroglioma is radioresistant. Of the blood-vessel tumours the hæmangioblastomas should be treated by operation and post-operative irradiation, while the malformations should receive irradiation alone. The meningiomas are radioresistant tumours. As to pituitary adenomas, their evolution could be divided into three stages : (*a*) endocrine, (*b*) visual, and (*c*) tumoral. The endocrine phase should be treated by radiation, the tumoral phase by surgery, and the treatment of the visual phase should be determined by the circumstances. Patients undergoing radiotherapy should be closely watched and surgical intervention undertaken when required. The best results follow combined treatment.

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Mr. GEOFFREY JEFFERSON : There are two points in Mr. Orley's remarks which call especially for discussion. First the need for histological control of specimens from tumours which have had radiation. This is quite true, and there is no doubt that material exists in this country waiting for observations to be made on it. Possibly one reason why it has not been done is that the records of other observations—and they have been made especially in America—do not indicate that it is a very fruitful field for study. In actuality only a handful of cases have been examined anywhere, and even in those where the greatest clinical improvement has followed X-radiation, the medulloblastomas, the tumour obtained at the eventual necropsy has shown remarkably little difference from the structure of the original biopsy. It is evident from this work that the relief that patients gain (when they gain anything) from post-operative X-ray treatment is due to a combination of factors, and that clear evidence of great alteration in tumour structure is not the only cause of this relief. Most clinicians will agree that radiotherapy has proved itself to be an advantage, and none will deny it to their patients in spite of the failure of scientific proof that it does a great deal to the tumour, so that the radiologist remains a valued partner.

The second point concerns the pituitary adenomas. I feel very strongly that operation and

not radiation is the essentially sound method of treatment, and I should reverse Mr. Orley's indications, believing that the small tumours are the most favourable for operation and the large ones more suitable for X-ray therapy. The operation mortality of the small tumours is not more than 2 or 3%. In one hundred operations on pituitary adenomas my own mortality is 7%, most of the deaths having occurred in the largest tumours. I have not found that much good follows radiation of the largest adenomas, those that one does not care to operate upon, and the probabilities are that they are not only dangerous to operate upon but impossible to cure by any means. I do not believe that it is wise to discuss this problem without reference to the visual fields, with the idea that pituitary adenomas could be schematized as all following one line of development and all appearing before the clinician at a uniform point in their development with the same visual changes in each. X-radiation seems to be the least use in the cases where one most wishes it to succeed, and that is a fact with a scientific meaning. It is not, however, a reason why we should stop trying.

Section of Surgery

SUB-SECTION OF PROCTOLOGY

President—J. P. LOCKHART-MUMMERY, F.R.C.S.

[*March* 8, 1939]

DISCUSSION ON MEGACOLON

Professor E. D. Telford: Constipation, associated with the radiological appearances of an enlarged colon and absence of gross organic obstruction, is found in patients of all ages.

It is tempting to regard the megacolon of adults as nothing more than a persistence of the congenital type. An obvious objection to this view is that whilst congenital megacolon is most common in male children (Finney [1] gives the proportion as seven males to two females) the adult megacolon is perhaps more often found in the female. It is likely that other factors, at present not fully understood, are at work in the adult cases, and such factors may be valvular obstructions, bands or adhesions.

I propose to speak mainly on the congenital megacolon of infants and children. Of the adult types I would merely say that in six cases which I have treated by lumbar cord-ganglionectomy, no benefit has resulted, and a like disappointing result has followed from the same operation in six cases of visceroptosis with obstinate constipation in young women.

The mechanism of intestinal peristalsis is still far from clear. Whilst we know that the smooth muscle of the gut is under the control of the autonomic nervous system, the extent of this control is not known. It is probably by no means complete; a considerable part is played by automatic action of the smooth muscle cell. The autonomic control is more akin to a governor rather than a prime mover. At present we believe that the dual innervation, sympathetic and parasympathetic, is of an antagonistic or complementary character. The sympathetic, by its control of sphincteric action, is the "filler" nerve, whilst the parasympathetic, by initiating peristalsis after relaxation of sphincteric control, is the "emptying" nerve.

Proper function depends on proper balance between the two, and disorder of function will result from imbalance. Although this is, no doubt, too simple and incomplete an explanation because there is evidence that nerve influence may alter according to the state of a viscus at any given time, there is nevertheless considerable evidence, clinical, operative, and experimental, to support the view that congenital megacolon is the result of autonomic imbalance and that it depends on achalasia, or failure of sphincteric action to relax.

The site of the achalasia may be at the pelvirectal junction—sphincter of O'Beirne—or at the anal sphincter. In the cases which I have examined at operation the former is the more common.

A second point, also obscure, is the cause of the achalasia. Is it in overaction of the sympathetic or underaction of the parasympathetic ?

The pathological anatomy of megacolon has been worked out by many observers. The changes are such as might be expected to result from distension and overwork—hypertrophy of all coats, chiefly by fibrous tissue, which squeezes out of existence the more highly specialized structures. This fibrosis is very important—it increases progressively with the age of the lesion and by gross and irrevocable alteration of structure it renders it more and more unlikely that operations on the nerve supply will be able to restore normal function. Hence, no doubt, the fact that these operations give their best results in the younger patients.

It is interesting to note that Finney [1], who gives a very detailed account of the histology, states that the plexuses of Meissner and Auerbach were normal.

The outstanding symptom is constipation, which, in the more severe cases, resists treatment by diet and purgatives and calls for regular enemata and, it may be, mechanical unloading of the lower bowel.

These children are invariably, as the result of the disease, undergrown, anæmic, of muddy complexion, and without interest in work or play, and markedly underdeveloped. Although constipation is common, some patients suffer from frequent small motions—sometimes a source of error in diagnosis. The scybalous masses cause a retention colitis with an overflow like that of a patient with prostatic retention. Examination of the abdomen shows distension and often large masses easily indented by the fingers. Sometimes the outline of a distended loop, usually the pelvic colon, can be felt, and may give a visible contour. The condition is sometimes confused with tuberculous peritonitis, because the soft distension, palpable tumour, and general malnutrition suggest a glandular mass.

Diagnosis is easily made by radiological examination, enema or meal. In this connexion it is well to remember that function is, after all, the true criterion, and from the standpoint of diagnosis and treatment alike should carry more weight than the X-ray evidence. For example, the barium enema gives a measure of distensibility rather than of function.

Very competent physicians have said that all these patients can be treated by medical means alone, but those of us who have had experience of the results of surgery will not agree with this. Many minor cases can be kept reasonably well by constant attention, but there remain the more severe cases which are intractable. The need for repeated enemata, often with mechanical unloading *per anum*, is an indication for surgery, as is also the retrogression of these children.

Surgical Treatment

In view of the successful results of sympathectomy, various operations, such as resection and short-circuits which have, in the past, been practised for this disease, are not likely now to be contemplated in the case of children.

The present method is by sympathectomy, and for this a knowledge of the course of the sympathetic supply is essential.

The sympathetic supply to the left half of the colon emerges from the spinal cord in the white rami of the lowest dorsal and 1st lumbar nerves. Wade [2] believes that they lie in the white ramus of the 1st lumbar nerve. The fibres pass into the ganglionated cord and shortly leave this to reach the front of the aorta. They leave the ganglionated cord between the 2nd and 3rd lumbar ganglia ; those of the left side passing straight to the aorta, whilst the fibres of the right side pass behind the vena cava to reach the front of the aorta. These medially directed fibres are known as the lumbar splanchnic nerves. On the aorta they form a loose plexus extending down to the origin of the inferior mesenteric artery. Here, after a thickening which contains ganglion cells, they pass as a perivascular plexus to the artery.

As a point of technique, operations to interrupt these fibres should be bilateral

in scope. Although good results have been claimed for operations limited to the left side, it is evident from the development of the colon as a medial tube that it must have a bilateral supply, and that division of its sympathetic supply must involve both sides.

The above description applies only to the area of colon fed by the inferior mesenteric artery, i.e. the left half from about the mid-point of the transverse colon onwards. Sympathetic denervation of the right half could be done only by a bilateral division of the great splanchnics, such as has been practised for arterial hypertension. Adson advises this in what he calls the more severe cases, but from my experience I doubt the need for so severe a procedure in the megacolon of childhood.

At what point, then, is it best to attempt the denervation of the left colon ? A variety of methods have been employed. These may be arranged in three groups.

Wade [2] has operated by section of the white ramus of the 1st lumbar nerve. Although this section would be beyond doubt preganglionic, the operation would be one of some difficulty, calling for an extraperitoneal posterolateral approach, and a bilateral section would be a serious undertaking in a child. Wade operated on the left side only.

The second available point for selection is through the lumbar splanchnics, and these can readily be divided on both sides by a transperitoneal approach. This method has been advocated by several writers, and is the one which I have always practised. It can be aptly described as simple and selective.

In view of the uncanny powers of regeneration possessed by the sympathetic system, it is probably better to remove that portion of the ganglionated cord from which the lumbar splanchnics arise. This is the explanation of the good results which many surgeons have obtained after a simple lumbar cord-ganglionectomy, the good result being, of course, due to the inevitable section of the lumbar splanchnics when the cord is removed.

The third point of attack is around the origin of the inferior mesenteric artery. Here, a patch of the aorta may be stripped, the ganglionated mass under cover of the artery removed, and a short length of the vessel stripped of its perivascular plexus. To these manœuvres, a deliberate section of the presacral nerve has often been added.

The third type is easy and is, of course, bilateral, but my objection to it is twofold. Firstly, interference with the presacral nerve will cause sexual disability in male children and, secondly, a too-energetic stripping of the inferior mesenteric artery may lead to section of the parasympathetic fibres which ascend from the pelvis.

Results of Sympathectomy

In an endeavour to estimate the results of division of the lumbar splanchnics for megacolon in children I have just completed a follow-up of cases operated on between 1932–36. I have taken no account of more recent cases where less than two years have elapsed since operation. I have been able to see nine children, five boys and four girls, their ages at the time of operation ranged from 4 to 16 years.

Of these nine children, six remain perfectly cured. Their bowels act without assistance, they are well grown, and normal in strength and energy. Two are not completely cured ; they still need assistance but not more than a twice-weekly dose of paraffin or mild laxative. One case has failed to benefit from the operation.

When the successful cases are examined by barium enema it is found that although function is perfect the colon remains enlarged, but not to the same extent as before operation.

Treatment by Spinal Anæsthesia Alone

Recent work, however, leads one to doubt whether laparotomy and sympathectomy are really necessary. Stabins, Morton and Merle Scott [3] have published a paper in which they show that patients on whom they had carried out a spinal

anæsthetic for diagnostic and prognostic reasons have remained "practically completely cured" without any operation. In order to try out this simple method I treated four cases of typical and severe megacolon by spinal anæsthesia alone between January and July 1938; they were three boys and one girl of ages from 9 to 13 years. The results have been remarkably good. All four cases have recovered normal function and remain well up to the present. The anæsthetic used was a solution of decicaine and in each case the level was up to the 3rd thoracic roots. It is not easy to explain these remarkable results. One can only say that the temporary paralysis of the sympathetic has caused the two halves of the autonomic system to come again into step.

These children will of course need to be watched for a much longer period, but the results so far obtained warrant a preliminary trial of spinal anæsthesia before considering the operation of sympathectomy.

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Professor J. Paterson Ross: (1) *Selection of cases of megacolon for sympathectomy.*—Operation should be performed only after conservative treatment has been given a proper trial, and only in cases in which the condition has been present since early infancy and in which the colon shows considerable dilatation. It is an additional point in favour of operation if the bladder and perhaps the ureters also show a similar neuromuscular defect—infrequent micturition with incomplete emptying of the bladder, and hydro-ureter.

Barium enema examination does not give as accurate an idea of bowel function as does a barium meal followed through, but the enema does give very valuable information about the degree to which the bowel may be distended without giving rise to the proper feeling of fullness which leads to a normal evacuation. This, combined with the reaction of the bowel to spinal anæsthesia, is of much value in selecting cases for sympathectomy.

(2) *The influence of age upon the recovery of the bowel*, as shown by radiographic examination.

It is well known that sympathectomy may often give symptomatic relief although the calibre of the colon remains much greater than normal. Recently papers, illustrated by radiographs, have appeared both here and in America showing that the size of the colon may be restored to normal by sympathectomy, but all these results were obtained in young children. This is only what one would expect from a knowledge of the pathology of the later stages of the disease, and it is an additional argument for early operation. Conservative treatment should therefore not be too prolonged; by the age of 5 or 6 years operation must be decided upon if it is to be really successful.

(3) *The nature of the upset in the autonomic balance.*—There seems to be little support for the view that megacolon is the result of true sympathetic overactivity. An error of development is more likely to be a defect rather than an excess of normal tissue or function, and the early onset of true megacolon suggests the possibility of a developmental error. Furthermore, the very limited portion of the bowel affected in some cases could hardly be oversupplied with sympathetic impulses without the rest of the large bowel showing more disturbance of its function. And I do not know of any evidence to show that the sympathetic system as a whole is overactive in cases of megacolon.

But a defect in the parasympathetic innervation is a more likely hypothesis. There is still considerable doubt as to the exact limits of the distribution of the vagus and the sacral autonomics. Where do the two nerve supplies meet ? Do they overlap ? May there be a gap between them ? Is there any individual variation in the portions supplied from above and below ?

Until our knowledge is more exact it may be reasonable to postulate that in cases of megacolon there may be a gap between the vagal and sacral supplies in which the sympathetic nerves provide the only extrinsic innervation of that part of the colon.

Whether this theory has anything in it or not it seems clear from a study of published cases that when parts of the bowel proximal to the sigmoid are involved the dilatation is not like that produced by mechanical obstruction in the distal colon. Dilatation of the colon may extend more and more proximally but always in continuity with the sigmoid dilatation ; and the distended cæcum and ascending colon so characteristic of chronic mechanical obstruction of the sigmoid is not met with unless the whole of the colon is affected.

(4) *The technique of sympathectomy.*—The assumption that we may be dealing with a gap in the parasympathetic supply (rather than a relative insufficiency) makes it all the more essential to plan a complete sympathectomy. If we operate on a plexus or on the branches of sympathetic trunks and ganglia we run the risk of missing some of them, and although I have not yet had the opportunity of carrying out radical splanchnic neurectomy for megacolon, this operation seems to me the most certain method of depriving the colon of its sympathetic supply. It is the same as the subdiaphragmatic splanchnic resection for hypertension, and I have been impressed by Adson's account of its good effect in megacolon involving the *whole* of the large bowel.

This operation, in which the three thoracic splanchnic nerves are divided where they pass through the diaphragm, and the upper two lumbar ganglia are excised (thus cutting off all the lumbar splanchnic supply), may be criticized on the ground that it sacrifices too much of the innervation of normal intra-abdominal organs and renders a male patient sterile. In my opinion it is not possible to carry out a complete sympathectomy of the colon and still preserve the nerve supply to the seminal vesicles, and the choice lies between trying to cure the disorder or trying to preserve the power of procreation. The loss of the other splanchnic nerves does not seem to be followed by any serious consequences—in fact the more radical operation gives a greater chance of cure without added risk or danger of complications. Since it sets out to cut deliberately nerves which can be clearly identified, since these nerves represent the roots rather than the branches of the sympathetic supply to the gut, and since they can be approached extraperitoneally and cut without apparent ill-effect upon the rest of the viscera innervated by them (always excepting the seminal vesicles) I feel inclined to use this method in future for the treatment of megacolon, except in those cases in which the sigmoid alone is involved when a more conservative resection of the lumbar splanchnic nerves should be sufficient.

Sir Lancelot Barrington-Ward : My contribution to this discussion is based on my experience with the congenital form of megacolon, which is a disease of childhood, sometimes hereditary, usually beginning in infancy, always affecting primarily the excretory part of the large bowel, the hindgut, and terminating fatally, if not relieved. My interest in the subject dates from the year 1910, when I was working with Sir William Arbuthnot Lane at the Hospital for Sick Children. With his great technical skill he performed several successful colectomies in these cases, but the results were disappointing, because the lower part of the pelvic colon and rectum had perforce to be left behind, and the disease was therefore not completeiy relieved. The operation was, however, occasionally successful. In 1928 Dr. Harris of Toronto

sent me an X-ray and report on a patient, a boy aged 3, whose colon Sir Arbuthnot Lane had excised when in Toronto in 1913. Dr. Harris re-examined him at the age of 18 and found him healthy and active, with no enlargement of the abdomen. His bowels moved once or twice daily and he never had to take purgatives.

In May 1928 I performed partial colectomy on a boy aged 8 and I have kept in close touch with him since. He has recently passed an Army medical examination for the Army Survey. One of my earliest cases of sympathectomy was a boy on whom I had performed a partial colectomy in 1928. The operation had improved his condition but he was still constipated at times. In 1932 I performed presacral neurectomy and inferior mesenteric ganglionectomy, and he has been quite healthy ever since.

More than two-thirds of my cases have been operated upon more than three years ago, and so there has been sufficient time to estimate the effects of the operation. I have operated upon 31 cases, of whom 24 are alive and well, seven are dead.

In considering the results it must be remembered that there has been no selection of cases ; any case considered an indubitable instance of congenital megacolon has been offered the chance of operation and many have been extreme examples, nor has tender age been a deterrent, for three were 6 months or under. Two had been previously operated upon soon after birth for supposed rectal atresia. No case was operated upon until all medical measures had been exhausted. The only mortality has been with presacral sympathectomy and that has been rather high. Why this technically more easy operation should have been more fatal than abdominal sympathectomy I do not know. Perhaps it is because coming early in the series they were worse examples of the disease with less experience in the operator. Two died of the operation, from pulmonary collapse and pneumonia respectively. Five died three months to one year after operation, from what might be described as mechanical causes. They were all instances of enormously distended colons which the least degree of constipation put in jeopardy. One case, three months after an apparently successful sympathectomy, was given a barium enema in my absence to test the radiological appearance of the bowel. The loop underwent rotation, and despite operation the patient died. Another case died after cæcostomy for intestinal obstruction, and three cases died following colectomy for recurrent volvulus.

The mortality 22·5% may seem heavy, but it must be remembered that this is a fatal disease if unrelieved. The surviving cases have all been most satisfactory. With two exceptions I have seen or heard from all the cases within the last year, and these two patients were extremely well three years after operation. The return of good function is the most certain expectation. The bowels move normally daily without medicine or with a mild and occasional laxative. It is interesting to observe that in some cases two or three weeks may have to elapse after operation before this is established. Abdominal distension takes longer to show any improvement. The younger the child, and the less the deformity, the better the result. An occasional relapse during the first few post-operative months is not uncommon. It is important at first to obtain a daily action of the bowels by a small dose of senna and paraffin. If more than two days elapse a small enema may be necessary, but after a few months of regular daily action, an artificial stimulus is rarely needed.

Certain interesting points emerge from the study of individual cases. That heredity plays a part is shown by the fact that one girl had an aunt who had been similarly afflicted and had died from the disease, and that two of this series are brothers with a third younger brother at home waiting operation. In early cases it is seen from the X-rays and barium enema and the operation findings that at this stage the disease is limited to the hindgut, from the junction of the middle and distal thirds of the transverse colon to the end of the rectum. Chronic obstruction in this segment leads to secondary dilatation of the rest of the colon and even the

ileum. For that reason I have never thought it necessary to divide the sympathetic supply on the right side.

SYMPATHECTOMY FOR HIRSCHPRUNG'S DISEASE—RESULTS.

Total : 31 cases

Alive and well 24
Dead .. 7

Sex

Males 21
Females 10

Age

Youngest 5 months
Oldest 11 years
Average 5 years

	Total	Died of operation	Died later	Relieved	Cured
Presacral sympathectomy	18	2	5	0	11
Abdominal sympathectomy	10	0	0	2*	8
Presacral and abdominal sympathectomy	1	0	0	0	1
Presacral sympathectomy and colectomy	1	0	0	0	1
Colectomy followed by presacral sympathectomy	1	0	0	0	1

*Too recent

Causes of death :

Operation .. .. 2 { Pulmonary collapse (1); Pneumonia (1)

Later complications 5 { Volvulus (1); Obstruction (1); Colectomy (3)

To conclude, I believe that the outlook for patients suffering from congenital megacolon has been greatly improved by the recent work on the sympathetic nervous system ; that abdominal sympathectomy is the better operation ; and that it should be performed before gross secondary changes have taken place in the large bowel.

Sir Arthur Hurst : I have seen 11 cases of megacolon in children, 9 of whom were boys and 2 girls, and 38 in adults, 20 of whom were males and 18 females.

Twenty-five years ago I suggested that the corresponding condition in the œsophagus was the result of absence of the relaxation of the cardiac sphincter which should normally occur as each peristaltic wave reaches it in the process of swallowing. Five years later I suggested that a similar absence of relaxation or " achalasia " of the anal sphincter was the cause of megacolon, and at the same time I expressed the belief that the two conditions would prove to be the result of some disturbance in the nervous control of the sphincters. This was demonstrated to be the case for mega-œsophagus by my former house-physician, G. W. Rake, in 1926. Since then inflammation or degeneration of the myenteric (Auerbach's) plexus has been found in every one of some 30 cases investigated by him and several other observers from this point of view (Hurst and Rake, 1930). Inflammation or degeneration of the plexus has been found in Hirschsprung's disease in children by Munro Cameron (two cases, 1928) and Robertson and Kernohan (" several cases ", 1938), and in the megacolon of adults by Etzel (eight cases, 1937).

Achalasia of the sphincter is sufficient to prevent the easy evacuation of fæces, which are consequently retained. Under normal conditions gas can escape from the rectum by voluntary relaxation of the sphincter at any time ; when achalasia is present voluntary relaxation is no longer possible, so gas as well as fæces accumulates in the rectum and pelvic colon.

The pelvic colon and rectum attempt to overcome the resistance offered by the closed anal sphincter by increased peristalsis with the result that their walls gradually become hypertrophied. This is at first sufficient to prevent any serious accumulation of fæces and gas, but after a time the amount of retention gradually increases. The thick walls of the fixed rectum give way less readily than the comparatively thin

walls of the freely movable pelvic colon, so that the rectum does not show the same degree of dilatation and in many cases it is only slightly enlarged.

The distension of the pelvic colon results in an increase in its length as well as in its diameter ; as it contains a great excess of gas the dilated and elongated loop rises during the day when the individual is in the erect position, and eventually its upper extremity generally reaches the left dome of the diaphragm.

If at the onset of dilatation of the pelvic colon the fold of mucous membrane at the pelvirectal flexure is unusually prominent, the dilatation of the part immediately proximal to it may exaggerate the kink and so prevent the passage of fæces and gas into the rectum. The primary condition is still the anal achalasia, but the secondary obstruction caused by the kink at the pelvirectal flexure prevents the entry of gas and fæces into the rectum, so that it does not share in the further dilatation of the pelvic colon.

The varying degree to which this secondary obstruction occurs accounts for the fact that in some cases the rectum is either not appreciably dilated or is only slightly dilated when compared with the pelvic colon. In spite of this it always appears much enlarged when an opaque enema is given. This shows that it must have been greatly distended at first, but that, when the pelvirectal kink developed and gas and fæces ceased to accumulate in the rectum, it contracted down without, however, losing the abnormal distensibility caused by the earlier distension. The valvular mechanism at the pelvirectal flexure is well seen when an opaque enema is given to a patient with megacolon : the fluid passes freely into the pelvic colon without any appreciable delay at the flexure, and no narrowing such as a sphincter would produce is observed, even in cases in which the rectum is only slightly dilated. The patient, however, often experiences great difficulty in evacuating all the fluid.

In the majority of cases the sigmoidoscope can be passed its full length of 12 in. blindly without meeting any resistance, whereas in normal individuals it is rarely possible to pass it beyond the pelvirectal flexure without having to withdraw the obturator and guide the instrument by direct vision. Endoscopy shows the end of the instrument in the centre of an enormous cavity. On withdrawing it no dividing line can be recognized between the pelvic colon and rectum, the dilatation of which extends to the entrance of the anal canal.

It is often assumed that a sphincter exists at the pelvirectal flexure. Sigmoidoscopy and radiography in normal individuals show, however, that there is never any constant constriction at the pelvirectal flexure such as would be produced by a sphincter, the lumen of the pelvic colon being separated from that of the rectum by the uppermost Houston's valve and by nothing else.

Every X-ray examination should begin with an inspection of the patient in the erect position before he has had an opaque meal or enema. The possibility of a megacolon is at once suggested by the discovery of eventration of the diaphragm.[1] The abnormally high position of the left dome of the diaphragm presents such a striking appearance that it can hardly be missed. It is generally possible in megacolon to recognize the outline of the enormously dilated air-containing loop of pelvic colon and to distinguish it from the gas-bubble in the fundus of the stomach, which is always limited below by the horizontal upper border of the shadow of the gastric contents. When a gas-containing cavity is seen under the right dome of the diaphragm as well as the left, the diagnosis of megacolon is certain.

An X-ray examination after an opaque enema is the only means of recognizing the exact anatomical condition present in megacolon. It is, however, essential to

[1] As the diaphragm in megacolon is displaced into what is normally part of the thoracic cavity, the condition may with justice be called eventration of the diaphragm, though this name is generally reserved for a condition in which the high position of the diaphragm is the result of a congenital defect in its musculature rather than of an acquired exaggeration in the upward thrust from below.

watch the fluid being run in, as it is otherwise impossible to interpret a radiograph owing to the large amount of overlapping of different segments of the bowel caused by the enormous dilatation of the pelvic colon. What is generally mistaken for a dilated splenic flexure is in almost every case the pelvic colon, which lies in front of and obscures a left colic flexure of more or less normal size.

The size of the colon as shown in a radiograph taken after the injection of an opaque enema is no guide to its actual size or its tonicity, but is an indication of its distensibility. The radiographic appearance after an opaque enema does not correspond with the condition present immediately before it is given, because the walls of the colon relax in order to allow more and more fluid to enter until the maximal size which has been present at any recent time is attained. This explains why the pelvic colon in a case of megacolon, in which more or less complete relief has followed treatment, often appears to be as large as ever when examined after an opaque enema, though any abdominal distension present previously may have disappeared and an opaque meal and sigmoidoscopic examination show no abnormality.

Megacolon is compatible with perfect health. In five of my patients the condition was accidentally discovered in the course of a routine investigation on account of abdominal symptoms caused by some other condition.

Toxic symptoms are rare unless aperients have been taken in excess. Megacolon does not appear to endanger life; 16 out of my 36 private cases were over 50 and an additional nine were over 40 when I first saw them, although the condition had presumably been present for many years, if not from infancy.

Only three of my patients died directly as a result of the intestinal condition—all after operation; a fourth patient died after excision of a carcinoma which had developed in the dilated colon. Of the three fatal cases a woman of 22 died after colectomy in 1912 and a boy of 5 died after ileo-sigmoidoscopy performed as a preliminary to colectomy in 1914. With our present knowledge of the condition I am sure that both of these patients could have been relieved by non-surgical means. The third case was a man of 55, who died after an operation for volvulus of the cæcum five years after non-surgical treatment had given him complete relief. At the post-mortem the rest of the colon was found to have contracted down to the normal size.

All the children with megacolon I have seen since the War are developing normally and appear to be none the worse either physically or mentally for having had a megacolon. One of them, who was first seen in 1923, when his pelvic colon was in contact with the right dome of the diaphragm above the liver as well as with the left dome, is now a well-developed young man of 24, whose bowels work regularly without artificial aid.

In a small proportion of cases the patient complains of sudden attacks of very severe pain with abdominal distension caused by the development of a partial volvulus of a loop of pelvic colon. Slight attacks in which the pain is not very severe and the distension is slight occur much more often; they are probably of the same nature. Both types of attack may last a few hours or a few days and almost always subside spontaneously. A man of 60, who had been operated upon in an attack in 1916 when a volvulus was reduced, had in the next ten years at least twenty equally severe attacks, for one of which he again underwent an operation though nothing was done. He has remained well since 1926 after having his anal canal dilated, and his bowels act regularly with the aid of nothing more than a daily dose of paraffin.

The main object in the treatment of megacolon is to lessen the resistance offered by the closed anal sphincter to the passage of fæces and gas. Rapid stretching of the sphincter is not as a rule effective, as it quickly contracts again to its original state. For a permanent result to be obtained the postural tone of the muscle-fibres of the sphincter must be permanently reduced. This can best be attained by the use of a conical vulcanite bougie which is passed every morning just after the first attempt to open the bowels has been made (Hurst, 1934). The bougie is pushed slowly in as

far as it will go without causing discomfort and kept in position for half an hour. Intelligent patients quickly learn to pass it for themselves, and the mother or nurse can pass it for children. A second attempt to defæcate is made immediately afterwards. At the end of about a week the bougie is kept in position for only a quarter of an hour; at the end of a month it is passed on alternate days, then once a week, and finally it is used only from time to time if a slight return of symptoms should occur.

When a child with megacolon comes under treatment, there is generally a large accumulation of fæces in the pelvic colon and in about 50% of cases in the rectum also. In adults such an accumulation is less often found. In both children and adults there is always a very large accumulation of gas in the dilated segment of bowel, the fæces and gas from which must be evacuated as completely as possible before any permanent improvement can be attained.

After the colon has been evacuated and the resistance offered by the anal sphincter reduced, the patient is generally able to get his bowels satisfactorily opened every day. No aperient should be given, but it is wise to prevent the fæces from becoming hard by means of liquid paraffin. In many cases no further treatment is required. Sometimes, however, especially if the dilatation has been excessive, there is still a tendency for fæces to accumulate in the pelvic colon in spite of the bowels being opened daily. It is then necessary to give an occasional enema.

In rare cases in adults it may become necessary to remove a loop of the pelvic colon which has formed a chronic volvulus and gives rise to frequent attacks of acute pain from partial obstruction. This was done with success during an interval between acute attacks in three of my patients.

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Mr. J. B. Oldham: I have myself treated by sympathectomy seven cases of Hirschsprung's disease and have had an opportunity, thanks to the kindness of my colleagues in hospital, of following six other cases throughout their treatment. Two of my cases are, I believe, the first to have been treated by sympathectomy on this side of the Atlantic. One of these is of special interest, as I have had the opportunity of following her case ever since she came into hospital in 1919, when I was a student and she was one of my patients. She was admitted with acute obstruction, a colostomy had to be done, and it was found that she was a marked case of Hirschsprung's disease and that the obstruction was due to a fæcolith 6 in. in diameter which was impacted in the lower sigmoid colon. A year later I returned to the hospital as a Resident and once more the patient was admitted—in fact, up till the beginning of 1929 she was more or less continuously in hospital. At one time or another she had performed on her almost every operation that had been suggested for the treatment of Hirschsprung's disease—the colon was plicated, both the anal and rectosigmoid sphincters were dilated, a colostomy was done, anastomosis made between the transverse colon and the rectosigmoid, and finally the sigmoid, descending, and left half of the transverse colon were excised. After all these operations she was still no better and on eight occasions, on account of subacute obstruction, I had to remove the impacted fæces under anæsthesia with the aid of a spoon. At the beginning of March 1929 I did a bilateral lumbar ganglionectomy on her and from that

day to this she has had no further trouble with her bowels. They have worked regularly every day without medicine or any special diet. She is now an extremely healthy and vivacious girl of 24 and the proud mother of two children.

I have tried at one time or another all the forms of sympathectomy which have been suggested. As a result of my experience in the treatment of Hirschsprung's disease, chronic constipation, and of sympathectomy for the treatment of other conditions, I have formulated for myself the following articles of faith :—

(1) I believe that those operations which aim at removal of the inferior mesenteric plexus or the presacral nerve should be abandoned. These operations are, particularly in small children, major undertakings. The operation is a delicate one and there is a risk of removing either too little or too much. If too much is removed we may damage the parasympathetic fibres or, in the male, we may destroy the patient's power of ejaculation.

(2) I can see no reason for any form of transperitoneal approach to the lumbar sympathetic. These operations involve large incisions with a definite risk of post-operative weakness or hernia of the abdominal wall. Much packing is needed to keep the abdominal contents out of the field of operation, and there is a subsequent risk of ileus or pneumonia.

(3) The operation should always be a bilateral one, for the left colon receives its nerve supply from both the right and left sides of the sympathetic. I am well aware that many successful cases have been reported following the removal of the left sympathetic fibres, but a study of the post-operative history of these cases shows that the results are not as good or as permanent as those produced by a bilateral operation. In my first case the immediate result following a left lumbar ganglionectomy was good, but after a few years the condition deteriorated. A right lumbar ganglionectomy was then done and the result has been excellent since then.

(4) While it must be agreed that Professor Telford's operation of removal of the lumbar splanchnics is the eclectic operation, yet I feel that the fibres are so small and vary so much in number and position that except in the hands of surgeons as experienced as Professor Telford there would be a great risk of leaving some of them intact. The only objection to removing the lumbar ganglia is that it results in vasomotor changes in the legs. I have never met any patients who complained of their legs being too warm after operation, though I know quite a few who have been very grateful for it.

(5) The ideal operation is a bilateral lumbar ganglionectomy done through an anterior, muscle-splitting approach. This operation is one of the easiest in surgery. The two sides can be done at the one operation and together need not take more than thirty minutes. The external oblique, internal oblique, and transversalis muscles are separated in the direction of their fibres. The peritoneum is pushed inwards and there is the sympathetic chain. The second and third ganglia are removed, the muscles and peritoneum are allowed to fall back into place, and the external oblique and skin are sutured. I have never seen any complications after this operation, which I have performed on 72 occasions. The patients are usually up at the end of four to six days and are out of hospital a few days later.

I am greatly interested in Professor Telford's experiences with spinal anæsthesia. I quite agree that a high spinal anæsthetic is less of an undertaking than any of the transperitoneal operations, but I am not convinced that it is as safe or certain as the extraperitoneal operation that I advocate. I yield to no one in my enthusiasm for spinal anæsthesia, and in the last fifteen years I have given nearly six thousand, but the thought of deliberately trying to anæsthetize the anterior spinal roots as high as the 3rd or 4th dorsal segment frightens me. I think there would be a risk especially in the small sickly patients suffering from megacolon, of the anæsthesia going up higher than was intended, with disastrous results.

As long ago as 1926 I tried this method unsuccessfully. One of my patients

came in with a fæcal impaction and in order to remove it a spinal anæsthetic was given. The effect on the bowel was so dramatic that I decided to repeat it after giving a barium enema. I admit that I do not know how high the anæsthesia rose, but as the X-ray taken after the anæsthetic shows the previously dilated and atonic bowel, contracting vigorously, the presumption is that it was high enough to block all the sympathetic impulses to the left colon. Dramatic though the immediate result was in this case, there was no permanent improvement, and in 1928 a lumbar sympathetic ganglionectomy was done with excellent results.

Section of Radiology

President—H. K. Graham Hodgson, C.V.O., F.R.C.P.

[*March* 17, 1939]

DISCUSSION ON KYMOGRAPHY

Dr. G. Simon: X-ray kymography is a method for studying the movements of certain organs, such as the heart, by means of a narrow radiotranslucent slit placed between the patient and the X-ray film.

The method was introduced by Sabat and Goett and Rosenthal in 1911. Further work on it was done by Knox in England just after the War.

Stumpf (1931), by introducing the multiple slit kymogram, advanced the method to the point of its being of value in clinical medicine. He, himself, says "the value and scope of the method is not yet clearly defined", and it is hoped that this discussion may help to indicate its value in clinical medicine somewhat more precisely.

Technique.—In this investigation a multiple slit kymogram was used. It consisted of parallel radio-opaque bars 1 cm. wide and the radiotranslucent space between each one was 0·5 mm. These were placed horizontally in relation to the thorax when the heart and mediastinum were under examination.

Tube film distance 3 ft. This short distance is no disadvantage, as the movement is rarely parallel to the slits, so the absolute distance of the movement is of no significance.

Ma. 60–120. K.V.P. 70–90.

Time.—This was controlled by the grid movement. A contacter is arranged so that the exposure is only on for 1 cm. of grid travel, and this avoids overlapping of the images. The rate of travel used was 1 cm. in 2–4 seconds, according to the pulse-rate of the patient. It is desirable to have two or three beats in each frame.

Two methods are used. In one, the film is fixed and the grid moved in front of it. Fig. 1 shows the resulting tracing. It is somewhat like a normal chest film, except for the notched edges of the heart shadow. This is the method of choice in cases of mediastinal neoplasm or aortic aneurysm.

In the second method the grid is fixed and the film moved behind it. This gives a more accurate analysis of the movements of the heart border at points placed 1 cm. apart. In this investigation it gave no additional evidence and so the moving grid method was used as it is easier to interpret.

Method of Interpretation: Anatomy and Physiology.

Fig. 1: This is a tracing of a young adult in good health. It is taken by the moving grid method.

The transverse lines indicate the end of movement of each bar, and the space between is given an arbitrary number.

From above downwards on the left border, Frames 4–7 show beats with a rapid out-thrust movement and slow recoil. These are typical of normal aortic pulsations.

By measuring the distances above each base-line the relative time relationship of the beats in different areas of the heart can be compared. The end of the out-thrust movement in Frame 5 (aorta) is definitely a little lower, i.e. later in time than the end of the out-thrusts in the ventricular area in Frame 19. This shows the end of the aortic out-thrust movement is during the medial or systolic movement of the left ventricle, as one would expect.

Frame 12 shows small rapid jerky movements out of phase with the ventricular movements. These are auricular or auricular appendage movements.

The left ventricle beats are well shown in Frame 17, and are characterized by a slow out-thrust or diastolic movement followed by a rapid medial movement, corresponding roughly to ventricular systole. Several types of ventricular movement are recorded in normal persons, and at the caudal part of the heart they are often rounded in shape.

On the right side movements are seen in the lower part which are ventricular in phase and character. It is possible that in the standing position the heart rotates a little and that then the lower right heart border is formed by the right ventricle. Alternatively, the right auricle beats are masked by transmitted pulsations from the right ventricle. Probably both events occur in normal subjects.

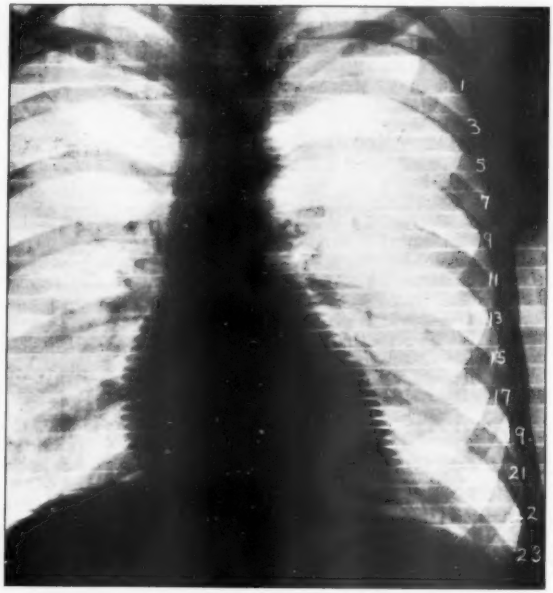

FIG. 1.—Normal kymogram. Young adult.

Hirsch (1934) has shown by some very neat experiments the time relationship of the movements on the kymogram to the electrical changes on the electrocardiograph, and heart sounds on the electrophonograph. It can thus be seen that kymography opens up a large field for physiological and anatomical research.

Clinical Application.

First I wish to demonstrate the possible value of kymography in the differential diagnoses of aneurysm of the aorta and mediastinal tumour. Kerley (1939) has stated that in 90% of cases there is no difficulty, so that leaves 10% in which this method may be of value.

First are some cases in which there is no difficulty, but I am showing them in order that we may appreciate the limitations and possibilities of the method.

Aneurysm of the Thoracic Aorta or Innominate Artery

Fig. 2 : A kymogram of a patient suffering from an aortic aneurysm. The chief features are :—

(*a*) On the right side vigorous pulsations in the region of the dilated ascending aorta (Frames 11–15).

(*b*) On the left side, practically no pulsations in the upper part, suggesting either the presence of a clot or that the movement is in a different plane from the grid.

(*c*) Vigorous pulsations are seen again lower down, which are aortic in phase and type. No normal descending aorta can be seen medial to the abnormal shadow.

Other cases of aneurysm in this series also showed areas which hardly moved at all. In no case of aneurysm was the aortic arch seen normally throughout its

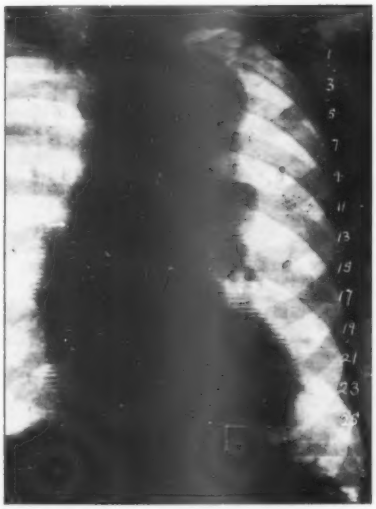

Fig. 2.—Aortic aneurysm.

Fig. 3.—Neoplasm.

whole extent. It either merged with the shadow mass or was abnormal where it could be seen beyond the main shadow.

Mediastinal Neoplasm

The majority of cases in this group showed either complete absence of pulsation, or very small jerky movements. The aorta could be visualized in parts by its shadow and movements independent of the tumour mass. Where it could be seen, it appeared normal. Sometimes a tumour showed vigorous pulsation.

Fig. 3 : A kymogram of a patient suffering from lymphadenoma, showing not only vigorous pulsations of the tumour edge, but bands of translucence across it during ventricular diastole. The pulsations in parts are aortic in phase and type, although actually the recoil movement is abnormally slow. In other parts the pulsations are flat-topped or small and jerky. This tumour disappeared following X-ray therapy.

This reveals that the kymogram gives no easy clue to the differential diagnosis, but may give information which is of importance.

The point to consider is: Can the pulsations of the normal aorta be seen through the opacity, or are they indistinguishable from the opacity?

Coming now to the difficult 10% the kymogram did decide this point and so help in the diagnosis of the following cases:—

L. B., male, aged 40.

Six months' history of pain in the back. Diagnosed clinically and on full X-ray examination as an aneurysm.

Kymogram fig. 4 shows very little pulsation in this massive opacity, but fig. 5 shows the undilated ascending aorta pulsations distinct from it, and this suggested a diagnosis of neoplasm, which was subsequently confirmed.

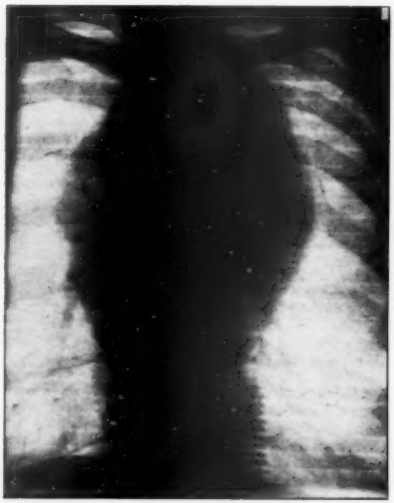

FIG. 4.—Neoplasm.

FIG. 5.—Neoplasm—oblique view. Arrows mark normal aortic pulsations.

S. A., female, aged 57.

Two years' gradual loss of voice, and pain in the upper chest. Treated as an aneurysm, but her condition deteriorated, and she began to lose weight. Plain X-ray showed a massive mediastinal opacity, but in spite of full radiological and clinical investigation there remained a doubt as to its nature.

Kymogram fig. 6 shows the normal aorta, and its pulsations seen through the opacity, and the oblique view showed pulsations against the back of the trachea, i.e. normal aorta, but none anteriorly. A diagnosis of neoplasm was therefore made, and this was subsequently confirmed.

There have been several other cases in this group where the kymogram gave additional information, which was of great diagnostic value. The information given in each doubtful case was much the same. Either the pulsations of the aorta could be picked up in a normal or displaced position, independent of the main opacity, when a diagnosis of neoplasm was suggested, or only abnormal aortic pulsations could be seen, which pointed to a diagnosis of aneurysm. The presence or absence of pulsation of the main opacity was not the deciding factor in any of these cases.

Cardiac Disease

Another possible sphere of usefulness for X-ray kymography is in cardiac disease.

We know from a study of the normal what types of normal pulsation the different heart chambers give, and so in some cases of cardiac disease it is possible to detect either abnormal pulsation or to demonstrate the extent of enlargement of the different chambers as revealed by their pulsations; this may be of real value to the clinician.

In *mitral stenosis* it has been found possible to analyse the bulge seen in the left border into that caused by enlargement of the pulmonary artery, when beats aortic in type and phase will be seen, and that caused by an enlarged left auricular appendage. In the latter case small rapid beats are seen, or if fibrillation is present, it may be relatively inert. It has also been found possible to confirm in the oblique view the posterior position of the enlarged auricle by its phasing in relation to the ventricle anteriorly. In cases where a double outline is seen in the anterior view, perhaps due to an enlarged left auricle, the different phasing has also been recorded, and so the nature of the shadow has been confirmed.

Fig. 6.—Neoplasm—Oblique view. Arrows mark normal aortic pulsations.

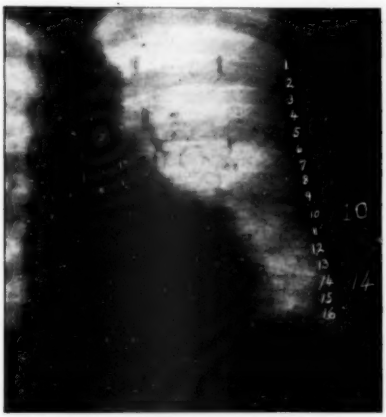

Fig. 7.—Myocardial lesion.

In *congenital heart disease* the kymogram has already given some interesting data, but we must await post-mortem or other proof before assessing its value in this realm.

Myocardial lesions.—Coronary occlusion or thrombosis with cardiac infarction and subsequent fibrosis.

I. F., male, aged 52.

Complaining of attacks of pain in the right wrist, arm, and mid-chest, which last about ten minutes.

Electrocardiograms showed development of an absent initial wave. T.1 and T.4 inverted, and later recovered. Diagnosed as a case of coronary thrombosis. Screening showed poor apical movements.

Kymograph fig. 7 shows an area in the left ventricle (frames 11-14) where the pulsations are greatly diminished. About 1 cm. medial to the left border pulsations can be seen which are somewhat better defined than those at the edge of the heart. It is just possible, therefore, the kymograph demarcates off the actual size of the area affected. This point will only be answered satisfactorily after post-mortem control of some of these cases.

A. S., aged 49.

Ten weeks ago sudden onset of bad pain in chest and down both arms.

Electrocardiograms showed changes which suggested a diagnosis of coronary thrombosis—? left ventricular aneurysm.

A kymograph (fig. 8) showed poor pulsations in the left ventricular area Frames 18–23. A more careful study shows inversion of form in Frame 17, i.e. rapid out-thrust and slow recoil. This suggests an area of fibrosis with passive movement instead of active muscular contraction. The appearances of the left border are in marked contrast to the normal pulsations on the right border and again medial to the edge of the poorly pulsating left border, one can see faintly on the original films pulsations of more depth and more normal form.

J. H., aged 56.

Ten weeks' pain in right side of chest. Dull ache worse on exertion.

Clinically no abnormality found, except an abnormal electrocardiogram indicative of coronary occlusion. The kymogram showed atypical beats in the left ventricular area, and he probably had a small anterior infarct.

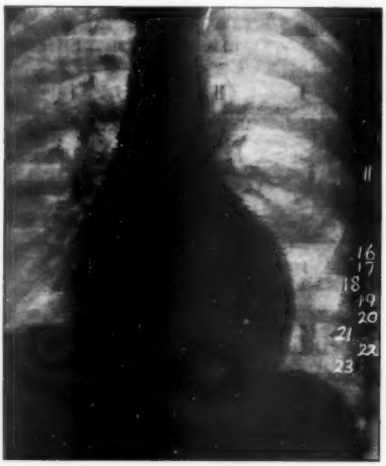

FIG. 8.—Myocardial lesion.

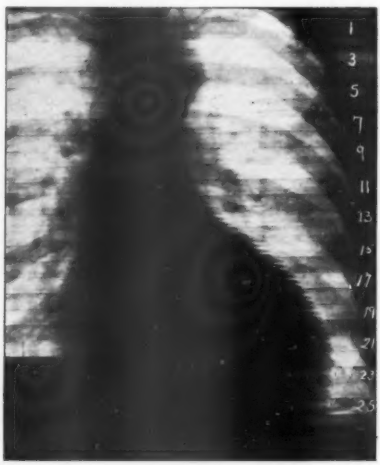

FIG. 9.—Same patient, one year later.

A kymogram one year later (fig. 9) shows that the wave form in Frames 19 and 20 area is still abnormal, and now the apical movements are greatly diminished. The electrocardiograph still showed inverted T waves in Leads I and II and also now in III.

The patient's condition has deteriorated. His attacks of anginal pain have become more frequent and his ability to take exercise has diminished. It seems probable that the kymogram by showing the atypical wave form followed later by diminished movement, is tracing out the deterioration of the myocardium in the region of the apex.

Pericardial disease.—The kymograph has been found of value in demonstrating pericardial adhesions. When these are small and adherent to the pleura, the beats tend to be drawn out over a small area. When they are large, or the pericardium is calcified, there will be diminished pulsation in the affected area. This may help the surgeon in planning his operation, by demonstrating the areas of restricted and free movement. It is quite easy to distinguish a hypertrophied heart from a small pericardial effusion, but the old enlarged and failing heart may show greatly restricted pulsations.

Other uses.—It can demonstrate the area of rigidity in œsophageal neoplasms and the movements of the diaphragm, and their possible relation to lung cavities.

I put forward a plea for the clinicians' co-operation in X-ray kymography, because only by this means can it become of any real clinical value. In no sense does kymography replace any of the existing methods of examination.

Summary.—The appearances seen on X-ray kymograms of normal heart are described.

The appearances seen in cases of aortic aneurysm and neoplasm are also shown, and how this method may be of help in the differential diagnosis of these conditions.

The changes in the pulsations in certain types of cardiac disease are also described.

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Dr. Ffrangcon Roberts (Abstract of paper published *in extenso* elsewhere): It is pleasant to recall that a member of this Society, the late Dr. Robert Knox, interested himself in kymography as long ago as 1925. With this exception radiologists in this country have only become interested in the subject within the last two years. Abroad, however, it has had exponents for some years in many countries, but it is to Stumpf and his associates that we owe the full development of the method. Not only have they applied kymography to every moving part of the body including the ureters, but they have devised a method, known as densography and based on the photo-electric cell, of subjecting the recorded movements to minute analysis and have also shown that these movements can be demonstrated in a kind of cinematographic form by a process which they call kymoscopy.

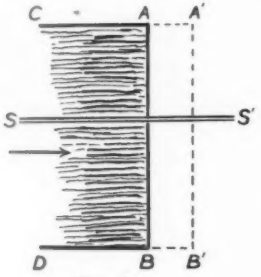

FIG. 1*a*.

FIG. 1*b*.

Based as it is on a classical physiological method, kymography would seem at first sight to be an ideal method of recording visceral movement, and I agree with Dr. Simon that it is of value in differential diagnosis. There are, however, certain fallacies which must be emphasized if its limitations are to be realized. These are due to two main causes. First the complexity of the cardiac movement and more especially the fact that the auricles are passengers in movements determined by the ventricles make it impossible to distinguish between active and passive movements. Secondly the kymograph can only record a movement as occurring in one direction only, the direction of the slits. Hence although the crests and troughs of the serrations give an indication of the size of the heart in diastole and systole respectively, the serrations themselves have no basis in reality and are no more than artefacts of the worst possible type. Imagine a body CABD (fig. 1*a*) moving to and fro in a

horizontal direction, the lines AB and A′B′ being the limits of movement. In front is a slit SS′ in an opaque sheet. The recorded movement on a film moving vertically is as shown in 1*b*, which is a true representation of the actual movement. If, however, CABD moves at an angle to the slit (fig. 2*a*) the recorded movement is as shown in fig. 2*b*, obviously a gross exaggeration and distortion of the true movement, the excursion and direction of which are A–A′ (fig. 2*a*).

Now imagine CABD shaped as in fig. 3*a* and moving upwards and downwards so that the edge AB moves to the position A′B′ and back. The point Y moves up

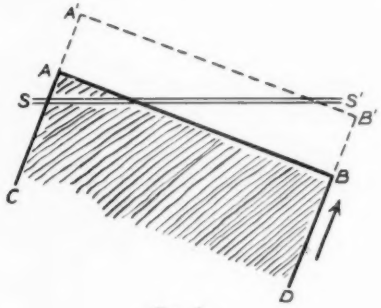

FIG. 2*a*.

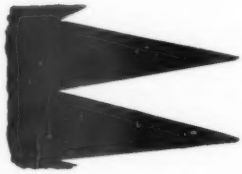

FIG. 2*b*.

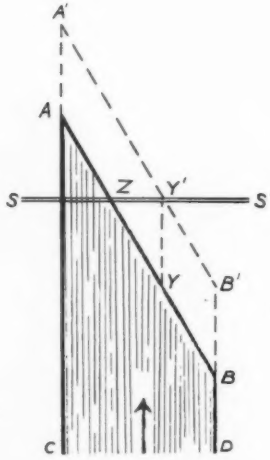

FIG. 3*a*.

FIG. 3*b*.

to the position Y′, but the movement recorded on the kymogram is a horizontal movement between Y′ and Z which appears as in fig. 3*b*. *But there is no horizontal movement. The kymogram therefore records a movement which does not exist.*

Numerous other illustrations could be given. Anyone can work them out for himself if he places objects of various shapes behind a narrow slit in a sheet of paper and observes how the movements of such objects would be recorded. It is only in the unusual case where the actual movement lies in the direction of the slit that the recorded movement faithfully represents the true movement. Under all other

conditions the record is a gross travesty of the true movement both in direction and magnitude. This statement holds equally whether the slit or the film is moving.

In order to confirm this statement I have constructed at the cost of a few shillings a kymograph with radial slits. The resulting kymogram is just what one would expect. At all points on the border of the heart the serrations are in the direction of the slits. The nature of the recorded movements, however produced, is determined less by the true movements than by the direction of the slits. These are simple facts of geometry which cannot be disputed. In view of the foregoing I cannot see how the serrations can be capable of the minute analysis to which Stumpf subjects them. I do not deny that within certain limits empirical deductions may be made from them, but I do emphatically deny that the serrations have any rational basis.

It might be thought that with the slit moving and the film fixed the kymogram records evenly the movement of successive points on the border of the heart. This is far from being the case. Let XY and X′Y′ (fig. 4) be the position of the border (in systole and diastole respectively) and let S_1 S_2 S_3 S_4 and S_5 represent successive positions of one slit such that S_1 and S_3 and S_5 record the position in diastole and S_2 and S_4 the position in systole. The border of the heart is thus represented on the

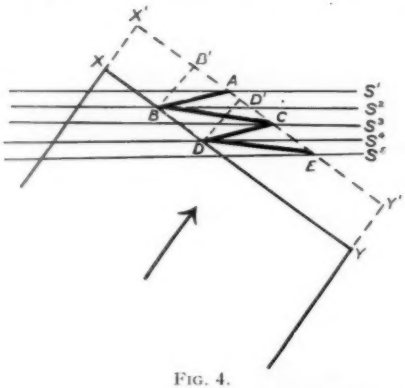

FIG. 4.

kymogram by ABCDE. But the point B in reality corresponds to B′ and D corresponds to D′. Therefore the kymogram records the movement of the surface in the following order: A–B′–C–D′–E. The above happens if the grid is moving slowly. If it moves rapidly a different error appears, as shown in fig. 5. Here A and C represent diastole and B, systole. But B corresponds to B′. It will be observed that the contraction A–B appears as a relaxation.

The kymoscope.—This is a simple device for reproducing in cinematographic form the movements of the heart as recorded by the kymograph. It depends upon two well-known principles: first, economy in drawing used to such effect in caricature whereby the artist puts in as little as possible leaving the reader to fill in the gaps from his imagination; secondly the retinal property of positive after-image upon which the cinema depends. The procedure is as follows. A film corresponding to the stationary grid is made so that the slits are transparent and the intervening parts opaque (fig. 6*a*). When one slides this film over the kymogram (fig. 6*b*) in the same direction as the grid moved when the kymogram was made, the movements of the heart are reproduced as in the cinematograph. All who have seen this effect will agree that it is both fascinating and realistic.

The question, however, arises, if the kymogram is, as we have seen, fictitious, does the kymoscope give a faithful representation of events? The answer is that it does.

The kymogram is fallacious because in looking at it we are observing something which we have no right to be observing *at the same time*. But if we place the slotted film (fig. 6*a*) over the kymogram (fig. 6*b*) our vision is reduced to a series of points on

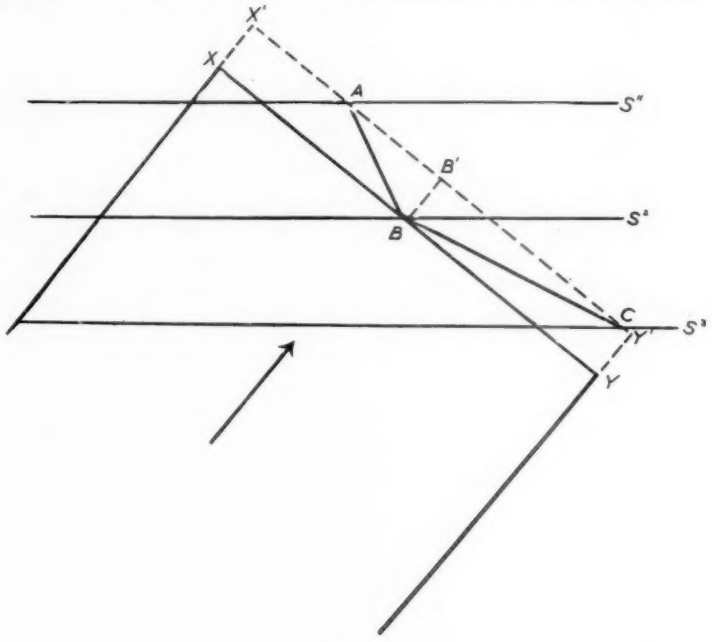

FIG. 5.

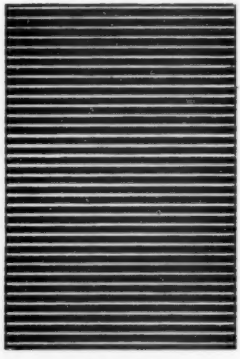

FIG. 6*a*.

FIG. 6*b*.

(*From Stumpf.*)

the heart's surface which is correct for one particular phase of the cardiac cycle. The delineation is incomplete, but the imagination fills up the blanks. If the slotted film be now moved over the kymogram successive scenes are presented to the eye

in their proper order, and the after-image of the retina produces the cinematographic effect. In other words, the observer is being made to see events as though he were in the position of the film when the kymograph was made. Thus the kymogram is completely untrue when viewed statically but perfectly true when viewed dynamically. The process is closely analogous to what occurs in television. Successful reception depends upon accurate co-ordination between scanning by the receiver and scanning by the transmitter. If this co-ordination is faulty there results the most fantastic distortion comparable to the distortion which I have illustrated above.

Conclusions.—(1) The kymograph within certain limitations is of value in determining the systolic and diastolic size of the heart and in the diagnosis of certain thoracic conditions, notably hilar shadows.

(2) The kymoscope is a reliable device which gives all the information which can be obtained from the X-ray cinema and does so far more cheaply than the latter. It would seem to have the further advantage over the cinema that slow-motion can be obtained from it. I think it is destined to replace the cinema.

(3) The serrations on the kymogram are fictitious, and incapable of any rational interpretation.

Dr. G. T. Calthrop showed a kymographic record of an iron bar which had been swung as a pendulum. It proved Dr. Roberts' point that the movements shown were not a true demonstration of the actual movements, but it also confirmed Dr. Simon by showing that the method worked. By moving a grid in front of a kymographic record of the heart of a patient, movements of the heart were shown on the screen. Kymographs were shown of a case of coronary thrombosis. There was an area at the apex of the heart at which the cardiac movements were absent. Two months later, with clinical improvement, the area affected was smaller. Another case was shown in which there was a bulge on the right contour of the heart. Kymographs in various positions proved conclusively that the bulge did not participate in the cardiac movements, and at operation a malignant growth was found spreading out from the mediastinum.

Dr. Peter Kerley: I experimented with the kymograph two years ago and am entirely in agreement with Dr. Simon that it is a most valuable method for the differential diagnosis of aneurysm and mediastinal tumour. It struck me, however, that there must be some fallacy in the interpretation of the cardiac pulsation as represented on the kymograph.

We know from fluoroscopy that quite apart from the intrinsic pulsation of the heart and the aorta, both organs move as a whole to the left side, yet the kymograph shows no sign at all of this lateral thrust. Dr. Roberts' experiments show very clearly the many fallacies of the method.

As regards the diagnosis of coronary thrombosis by the kymograph, we know very little about the pulsation of the affected area. There may be diminished pulsation but there may be normal pulsation, or there may even be increased pulsation. The cases showing diminished pulsation are probably those in which there is a sharp pericardial reaction with resulting pericardial adhesions. It will need much more evidence than has already been accumulated to prove that an area of diminished pulsation on the kymograph represents a cardiac infarct.

Dr. J. V. Sparks: I would like to have heard more details about the kymoscope, as I understood that by this method one could place the film in a viewing box, with a suitable grid, and study the movements at varying speeds, comparable to a slow-motion fluoroscopic examination. As far as I can judge, from what Dr. Roberts said, this method does not appear to give so much information as I had anticipated.

I would like to emphasize that it is incorrect to imagine that a mediastinal neoplasm can be differentiated from an aneurysm, by screen examination ; and that a mediastinal mass, showing marked, visible pulsation, is much more frequently due to neoplasm than to aneurysm of the aorta. The information obtained on the cases which I submitted to Dr. Simon for kymographic examination has proved correct in every instance.

Here are two cases illustrating the advantages of this method. The first case shows a large mass in the anterior mediastinum, projecting to the right of the midline. This mass had been discovered accidentally during an X-ray examination for injury to the ribs, in a woman aged 40. She had complained of attacks of dyspnœa and palpitation. The initial diagnosis was aneurysm ; subsequently she underwent a full course of X-ray therapy, and the size of the mass remained unaltered. Kymographic examination showed that the mass was non-pulsatile, and subsequently a mediastinal cyst was removed by Mr. Tudor Edwards.

The second case is that of a mass in a woman aged 45, projecting to the right of the manubrium, in the anterior mediastinum, where an operation was performed for the removal of a " dermoid cyst ". At the operation difficulty was experienced in separating the mass from the mediastinum, and the patient died following puncture of an aneurysm of the ascending aorta. I feel confident that had kymography been available in this case it would have revealed the true diagnosis.

Dr. Franklin Wood : I am glad that Dr. Simon has suggested that the left auricle forms a small part of the left border of the heart. This is a matter that has often been discussed and kymography appears to give a definite answer since auricular pulsations can be seen in a limited area below the pulmonary conus. In patients with mitral stenosis they are increased and can be observed passing downwards into the ventricular area.

As regards the right border of the heart, it is true that in about 50% of the cases the pulsations are ventricular in type, but this does not necessarily mean that the right ventricle is visible on this border of the heart. It might be explained by the fact that the movements of the auricle are often so rapid that they are not visible owing to the relatively slow rate of travel of the grid ; in many cases, however, a distinct notch representing auricular systole, can be made out.

The employment of a 3-ft. focal-film distance is a retrograde step. It is quite possible to obtain kymograms at 5 ft. in patients of normal density with apparatus of suitable output using fast intensifying screens. The value of kymography in the differential diagnosis of aneurysm and new growth has been much stressed recently. This is unfortunate, since whilst it was of undoubted value in these cases, its use in other types of examination may be ignored. In the differential diagnosis of aneurysm and new growth, tomography may be found to be as valuable a procedure as kymography.

Section for the Study of Disease in Children

President—E. A. COCKAYNE, D.M.

(*February* 24, 1939)

Polyuria of Unknown Origin.—H. L. ELLIS, L.R.C.P., M.R.C.S. (by permission of Dr. W. PEARSON).

Female child, aged 4 years, admitted to hospital on account of excessive thirst and polyuria. Onset at 16 months following measles. Intake varied at home between 50–70 oz. a day with corresponding big output. Makes use of every opportunity to get fluid, and whilst in hospital on unlimited intake drank on one occasion five and a half pints in twenty-four hours. Appetite is fair, providing she has at least 30 oz. of fluid *per diem*. At times appears to have difficulty in swallowing, but only when given normal fluid intake.

On examination.—A well-built child but small for her age. Height 2 ft. 10 in. Except for internal strabismus and at times protuberant abdomen nothing abnormal found.

On measured fluid intake, no response when given: (*a*) Salt-free diet; (*b*) measured salt; (*c*) pituitrin.

Blood urea per 100 c.c.: 48 mgm.; 39 mgm.; 26 mgm.; 31 mgm.

Blood calcium: 9·2 mgm. per 100 c.c. Inorganic phosphorus: 4·0 mgm. per 100 c.c. Plasma phosphatase: 8·4 units.

Urea clearance test: 106% (normal).

Urine: Nothing abnormal on biochemical and pathological examination. On one occasion trace of albumin was found, 10 mgm.%.

X-ray examination of skull and long bones: Nothing abnormal.

Cerebrospinal fluid: Nothing abnormal. Wassermann reaction negative.

Case of Glomerulonephritis eleven years after double Edebohl's Operation.—R. S. ILLINGWORTH, M.R.C.P. (by courtesy of Dr. FREW).

Female, now aged 19, first attended the hospital on 11.10.27 with a history of puffiness of the feet and ankles of three weeks' duration. There had been some oliguria for three weeks: four days before admission the child seemed feverish and ill and complained of generalized pains. Two days before admission there was slight vomiting. No history of preceding infection.

Previous history.—No scarlet fever or history of sore throats.

On admission.—Rather drowsy, pale ; impetigo round mouth ; pitting œdema of legs. No œdema of face ; tonsils slightly injected ; some enlargement of tonsillar glands.

Urine : Albumin +++. White cells a few. No casts or red cells. Discs normal.

Progress.—17.11.27 : No œdema, child well.

22.11.27 : Exacerbation. Child very drowsy, vomiting, marked generalized œdema. Blood-urea now 107 mgm.%. Blood-pressure 90/40. Urine output 6–12 oz. per day. For the next six weeks there was frequent vomiting and persistence of œdema ; blood-urea rose to 163 mgm.%.

2.2.28 : Œdema now very severe : pitting œdema over abdominal wall and in limbs. Ascites present. Cannot bend knees on account of œdema.

20.2.28 : Abdomen tapped—12½ pints removed.

9.3.28 : Decapsulation of kidneys considered. Abdomen tapped—fluid "like a mixture of water and milk." Dullness at both lung bases. Blood-urea now 54.

17.3.28 : Decapsulation of both kidneys by Mr. O. L. Addison, by transperitoneal route. Capsules quite loose and stripped readily. Kidneys large and smooth ; no scarring ; stellate veins not prominent.

20.3.28 : Œdema decreased ; blood-urea 54 mgm.%. "Œdema has left face and upper limbs, revealing her as grossly emaciated."

2.4.28 : Very œdematous again. Blood-pressure 110/80.

24.4.28 : Abdomen tapped—20 pints removed.

15.5.28 : Abdomen retapped. Blood-urea 62 mgm.%.

13.6.28 : Abdomen retapped.

13.10.28 : Still marked œdema of face, back, and legs.

18.1.29 : Now sitting up out of bed. Ascites still present ; no œdema elsewhere ; trace of sugar in several specimens of urine.

28.3.29 : Discharged to convalescent home with no œdema.

Special Investigations (Blood Urea mgm.%)

23.11.27	107	26.6.28	67	21.8.28	62	20.11.28	41
20.12.27	77	3.7.28	83	28.8.28	93	27.11.28	48
31.1.28	37	10.7.28	60	4.9.28	62	11.12.28	51
28.2.28	39	17.7.28	56	25.9.28	63	18.12.28	47
27.3.28	75	24.7.28	61	2.10.28	72	2.1.29	43
24.4.28	64	31.7.28	87	12.10.28	70	22.1.29	44
30.5.28	73	7.8.28	63	30.10.28	43	13.2.29	49
12.6.28	79	13.8.28	111	6.11.28	55	18.3.29	44
19.6.28	71	15.8.28	83	13.11.28	41		

Œdema fluid (16.5.28) : Urea 79 mgm.% ; sugar 0·069% ; chlorides 0·643% ; uric acid 3·5 mgm.% ; phosphates 5·04 mgm.% ; cholesterol 45 mgm.%. Proteins : Albumin 0·17% ; globulin 0·061%.

Urine (17.10.27) : Specific gravity 1026 ; albumin +++ ; W.B.C. few. No casts.

9.3.28. Albumin +++. No report re deposit.

30.6.28 : Albumin +++. W.B.C. +. R.B.C. very few. Casts : hyaline + ; granular few ; waxy few ; cylindroids +. Sugar, slight trace.

Urea Concentration Tests

		Specimen A	Specimen B
17.1.28 :	Albumin	+++	+++
	Volume	310 c.c.	42 c.c.
	Specific gravity	1013	1015
	Urea	2·36%	2·46%
		Urea %	Urine c.c.
20.1.28 :	Before urea	2·11	—
	1st hour	1·98	29
	2nd hour	2·54	15
	3rd hour	2·35	19
30.3.28 :	Before urea	1·81	—
	1st hour	1·70	14
	2nd hour	1·97	30
	3rd hour	1·65	9
30.6.28 :	Before urea	1·46	—
	1st hour	1·60	21
	2nd hour	1·72	29
	3rd hour	1·59	26

Urine output: November 1927, 6 to 12 oz. March before decapsulation, 6 to 12 oz., after unchanged. July 1928, 8 to 16 oz. March 1929, 20 to 40 oz.

Temperature normal throughout.

On re-examination (18.1.39).—Patient was very well indeed: there had been no relapses since discharge from the hospital: the patient was at work and free from symptoms.

Present age 19. Weight 9 st. Blood-pressure 125/85. Blood-urea 29 mgm.%. Urine: Specific gravity 1016; albumin 70 mgm.%; no sugar; no casts or cells in deposit.

Dictyocytic Reticulosarcoma.—D. G. ff. EDWARD, M.D. (by courtesy of Dr. D. PATERSON).

Boy, aged 5½ on 23.9.38 when first admitted to hospital under Dr. Paterson.

History.—Pyrexia, swelling of abdomen, anorexia, loss of weight and headache following upon pertussis five months previously.

On examination.—Pale and sallow. Irregular pyrexia up to 103° and tachycardia. Liver enlarged two fingerbreadths below costal margin and spleen to level of umbilicus. Hard fixed mass of lymph-glands in left iliac fossa and on left lateral wall of pelvis (felt *per rectum*). No enlargement of superficial lymph glands.

Investigations.—Blood-count: R.B.C. 3,270,000; Hb. 45%; C.I. 0·7; W.B.C. 5,600 (polys.; 78%; lymphos. 13%; monos. 7%; eosinos. 1%; basos. 1%).

Urine: A few R.B.C. in the deposit.

Mantoux reaction: Doubtful, weak, positive.

X-ray examination: Chest and pelvis normal.

A diagnosis of Hodgkin's disease was made, but a biopsy was not done, owing to the absence of a suitable superficial lymph-node, and the patient was discharged on 17.10.38. He was readmitted on 26.12.38 because of hæmoptysis. The physical signs were similar except that there were now a few enlarged glands in the right groin.

Further investigations.—Blood-count: R.B.C. 1,800,000; Hb. 32%; C.I. 0·9; W.B.C. 3,650 (polys. 43%, lymphos. 44%, monos. 12%, myelos. 1%). Reticulos. 0·1%. Platelets 196,000.

Erythrocyte sedimentation rate 59 mm. (one hour).

Wassermann reaction negative.

Van den Bergh reaction : Very faint delayed direct. Total of 1 unit.

X-ray examination : chest, long bones and spine normal.

Biopsy : Section of lymph-node from right groin showed the normal architecture to be lost with replacement by polygonal cells with rather small darkly staining nuclei separated by an intercellular substance containing fibrils. A few small "giant cells", some binucleate, were present, but they in no way resembled the Sternberg-Reed cells of Hodgkin's disease (fig. 1). Mitoses were very scanty. Staining with van Gieson showed no new formation of collagen, but special staining for reticulin demonstrated plentiful reticulin fibres in the intercellular substance (fig. 2). The histological appearances, therefore, are not those of Hodgkin's disease and the condition is to be regarded as a dictyocytic reticulosarcoma, a primary tumour of the reticulo-endothelial system showing differentiation into reticulin fibre-forming cells.

Treatment and progress.—He has been treated by blood transfusions and deep X-ray therapy. This has produced improvement with shrinkage of the iliac glands and, to a less extent, of the spleen. The patient has also appeared brighter and his temperature has been lower.

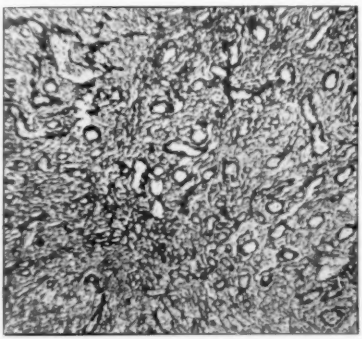

FIG. 1.—Stained with hæmatoxylin and eosin. × 300.

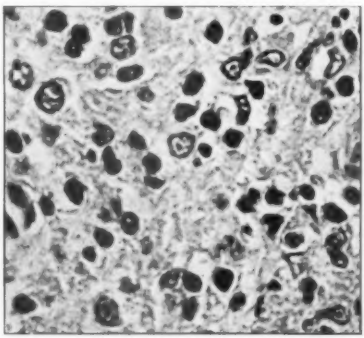

FIG. 2.—Stained to demonstrate reticulin fibres. × 90.

Comment.—It is suggested that the histological appearances are those of a dictyocytic reticulosarcoma. This name was first employed by Géry and Bablet (1935), and has more recently been used by Robb-Smith (1936 and 1938) in his classification of the lymphadenopathies for one type of differentiated reticulosarcoma. None of the recorded cases appears to have occurred in children. The need of a biopsy in all obscure cases of lymphadenopathy and possible Hodgkin's disease is emphasized. Only by accurate histological diagnosis of each case can more be learnt about the incidence, natural history and response to treatment of these recently recognized conditions, frequently in the past called "atypical Hodgkin's disease."

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Subarachnoid Hæmorrhage.—E. A. COCKAYNE, D.M.

Female infant, aged 11 months. One week's history of transitory attacks of vomiting, pallor, and limpness. On the evening of admission remained unconscious after one of these attacks.

On arrival.—Comatose with a bulging fontanelle ; flexion of neck was not resisted but produced flexion of hips. No other neurological signs. Temperature 101°. Pulse 104. Profuse retinal hæmorrhages in both fundi, many subhyaloid. No swelling of discs.

Cerebrospinal fluid : Pressure over 300 mm. Densely blood-stained.

The day after admission the infant had a right-sided fit lasting a few hours. During this seizure the cerebrospinal fluid was found to be less blood-stained than before. Since then there has been an uneventful recovery, and she now seems perfectly well. Cerebrospinal fluid obtained nine days after admission was only slightly blood-stained.

Wassermann reaction of original specimen of cerebrospinal fluid negative. Bleeding and coagulation times normal. Full blood-count (including platelets) normal.

[*March* 24, 1939]

Familial Hepatitis and Chronic Jaundice

By Professor ROBERT DEBRÉ (Paris)

Abstract.—The author reports the history of a family of six children, of whom two, the eldest and the fifth, are normal ; three died, a boy when 6 months old and two girls when 9 and 10 years old, from the same familial disease that also attacked another boy now 7 years old. The essential features of this disease are hypertrophy of both liver and spleen, chronic icterus with evidence of salts and bile-pigments in the blood and urine, retardation of physical, mental, and sexual development, slight deafness in one case and clubbing of the fingers in another. This condition is a good example of biliary cirrhosis of the liver.

After reviewing recent French observations, the author recalls the large contribution of English authors on the subject.

He then distinguishes three types of familial cirrhosis : Laennec's type with enlarged liver, the type of splenomegalic anascitic and anicteric cirrhosis, resembling Banti's syndrome, and the commonest type or biliary cirrhosis.

The author describes particular histological lesions, and when dealing with differential diagnoses, excludes dyslipoidic, polycoric, and other acquired cirrhosis in children. He then summarizes the relationships between this disease and the obstructive cirrhosis due to a congenital defect of the bile-ducts, the cirrhosis in young Indians, the syndrome of hepatic lenticular degeneration, and the syndrome of cirrhosis of the liver combined with hæmangiomatosis. Finally, after recalling the close analogy of the condition with renal dwarfism, the author shows how the interpretation of these relationships may throw light on the pathogenesis of various progressive congenital diseases.

RÉSUMÉ.—L'auteur rapporte l'histoire d'une famille de six enfants, dont deux, l'ainé et le cinquième, sont normaux et trois, un garçon de six mois et deux filles de 9 et 10 ans, sont morts de la même maladie familiale qui a maintenant atteint un garçon de 7 ans. Les caractères essentiels de cette maladie sont une hypertrophie du foie et de la rate, un ictère chronique avec des sels et des pigments biliaires dans le sang et les urines, un retard du développement corporel, mental et sexuel, une légère surdité dans un cas et de l'hippocratisme digital dans un autre. Cette affection est un bon exemple de la cirrhose biliaire du foie.

Après une revue des observations françaises récentes, l'auteur rappelle la grande contribution des auteurs anglais à ce sujet.

Il distingue ensuite trois types de cirrhose familiale : le type de Laennec, le type de cirrhose sans ascite et sans ictère, ressemblant au syndrome de Banti, et le type le plus fréquent, c'est-à-dire, la cirrhose biliaire.

L'auteur décrit les lésions histologiques spéciales, et, en parlant du diagnostic différentiel, élimine les cirrhoses dyslipoïdiques, polycoriques, et les autres cirrhoses acquises de l'enfance. Il résume ensuite les relations entre cette maladie et la cirrhose obstructive par défaut congénital des voies biliaires, la cirrhose des jeunes Indiens, la dégénérescence hépatolenticulaire et le syndrome de cirrhose hépatique avec hémangiomatose. Finalement, après avoir rappelé l'analogie proche de cette maladie avec le nanisme rénal, l'auteur démontre comment l'interprétation de ces relations peut éclairer la pathogénèse des différentes maladies congénitales progressives.

ZUSAMMENFASSUNG.—Verf. berichtet über eine Familie von sechs Kinder, von denen das erste und das fünfte normal sind und drei, ein Knabe im Alter von 6 Monaten und zwei Mädchen im Alter von 9 bzw. 10 Jahre, an derselben Krankheit gestorben sind, die ein weiteres Kind, u. zw. einen jetzt 7 jährigen Knaben befallen hat. Die wesentlichen Kennzeichen dieser Krankheit sind Leber- und Milzschwellung, chronischer Ikterus mit Anwesenheit von Salzen und Gallenfarbstoffen im Blut und Harn, Zurückbleiben der körperlichen, psychischen und sexuellen Entwicklung, leichte Schwerhörigkeit in einem Falle und Trommelschlägelfinger in einem anderen. Dieser Zustand ist ein gutes Beispiel der biliären Leberzirrhose.

Verf. gibt eine übersicht über die französische Litteratur und erinnert daran, in welch erheblichem Maasse englische Autoren zur Kenntnis dieser Frage beigetragen haben.

Er unterscheidet drei Typen von familiärer Zirrhose : den Laennecschen Typ, mit Hepatomegalie, die splenomegalische Zirrhose ohne Ascites oder Ikterus, dem Bantischen Syndrom gleichend, und den gewöhnlichsten Typ : die biliäre Zirrhose.

Verf. beschreibt die besonderen histologischen Veränderungen. Bei der Differentialdiagnose schliesst er die dyslipoidischen, polykorischen und andere erworbene Zirrhosen des Kindesalters aus. Es folgt dann eine Zusammenfassung der Beziehungen zwischen dieser Krankheit und der durch angeborene Defekte der Gallenwege bedingten obstruktiven Zirrhose, der Zirrhose bei jungen Indern, dem Syndrom der hepatolentikulären Degeneration und dem Syndrom der Leberzirrhose mit begleitender Hämangiomatose. Zum Schluss erinnert Verf. an die enge Analogie zwischen diesem Zustand und dem renalen Zwergwuchs und zeigt inwiefern die Deutung dieser Beziehungen die Pathogenese verschiedener progredienter angeborener Krankheiten dem Verständnis näherbringen kann.

CIRRHOSIS of the liver is not a common disease in children, but it is interesting because its study illustrates the relations and contrasts between hereditary and acquired lesions. Until recently authors have been in the habit of explaining the ætiology of cirrhosis by seeking its causes among the infections or intoxications suffered by the patient, e.g. syphilis, tuberculosis, alcoholism, &c., and if no exogenous factor can be found they fall back upon an endogenous intoxication of splenic or intestinal origin. Here, as in other problems, the study of children's diseases helps us. When cirrhosis of the liver attacks a child during the first months of its life, and when after a single case of cirrhosis another brother or sister, and possibly even several brothers and sisters are similarly attacked, does not that suggest the possibility that we are dealing with a disease hereditary in origin ? The following is an account of a family whom I have known for the last twelve years.

The father, a delicate man, is said to have had repeated bilious attacks, but when recently examined he had neither icterus nor hepatic cirrhosis. The mother is well and has had six uneventful pregnancies. During her second pregnancy she became jaundiced, and although all examinations of both children and parents were negative and no syphilitic stigmata were present, she underwent a novarsenobillon and bismuth treatment. She has never had a miscarriage. When examined she had neither icterus nor cirrhosis. The family history of both parents was negative.

Odette, the eldest child, born in 1914, is healthy and perfectly normal.

The second child, Albert, born in 1921, we never saw. He is said to have had subicterus, but no tendency to hæmorrhage. He increased in weight slowly and died at the age of 8 months from "wasting and diarrhœa". The family doctor is said to have ascertained that his liver was enlarged.

The third child, Gisele, of normal weight at birth, had gastro-enteritis at 3 months. She became permanently jaundiced, suffered from intense pruritus, and had brownish urine and colourless stools. Later she lost weight and was below the average in height and was also very backward mentally. She did not walk until she was over 3. This child was under our observation for five years. During that time all the above-mentioned symptoms persisted. The liver was hard, smooth, painless, and enlarged; its sharp lower edge could be felt one fingerbreadth above the umbilicus; the spleen was smooth, hard and enlarged, and extended below the short ribs. The fingers were clubbed and the child was slightly deaf. Chemical examination of the blood, urine, and fæces, confirmed the diagnosis of icterus with retention of bile salts and pigments. R.B.C. 3,000,000; Hb. 70%. Fragility test increased. Her weight remained stationary at 17 kg. and at 9 years of age she was the size of a 6-year-old child. She then had hæmorrhages from the gums and for this reason certain teeth which should should have been extracted were allowed to remain. She died at the age of 9 from bronchopneumonia.

The fourth child, Fochette, was 1 year of age when first seen. The liver is said to have been normal during the first weeks of life, but when 2 months old she became slightly jaundiced for a fortnight. At 6 months she had pruritus, pale stools and dark urine, but no anorexia or icterus. When first seen the liver was smooth, hard, painless, and extended down to the iliac spine. The spleen was smooth and hard and could be felt enlarged below the costal margin. Blood examination showed increased bilirubin (25 instead of 5 by Mellengracht's method). R.B.C. 3,700,000; Hb. 80%. Fragility test increased. Urine analysis showed traces of bile salts. Again we noticed retardation in weight, height, and mental development. The child could barely sit up when she was 18 months old; she began to walk at 2½ years and did not talk till still later. Like her sister she never weighed more than 17 kg. She died at the age of 10 with ascites, hæmorrhages from the gums and from the site of an injection and an uncontrollable hæmorrhage from a slight skin lesion.

Both these girls underwent a long treatment for syphilis which was badly tolerated and gave no benefit.

The fifth child, Ginette, born in 1927, developed normally and has had no pathological symptoms.

Jean, the sixth child, was born in 1932. During pregnancy his mother underwent an arsenobismuth treatment of great intensity and doubtful justification. His weight at birth was 4 kg. The child fared well until December 1935 when he began to suffer from spontaneous epistaxis, which was more frequent when at rest. The parents also noticed the deep colour of the urine. In February 1936 colourless stools and pruritus were observed. In March a physician who was consulted noticed that the liver extended below the false ribs. He ordered calomel. Icterus began in May 1936. Two months later the liver extended to two or three fingerbreadths below the costal margin and the spleen was slightly enlarged. A syphilologist examined the child and prescribed two courses of 20 intramuscular injections of bismuth. After the nineteenth injection there was an outbreak of scarlet fever with intense rash but no complications. The second course of bismuth injections was given between November 1936 and January 1937. Since then the child's condition has remained much the same: Icterus, pruritus, deep coloration of the urine varying in intensity, lack of colour of the stools—this last feature being only partial. (The boy's sisters had stools of a white putty colour.) The appetite is poor. In February 1937 the child was brought for the first time for examination at my hospital. He was 5 years old, normally developed, and weighed 18·450 kg. The skin and conjunctiva were definitely icteric. We noticed scars left from scratching. The enlarged liver extended three fingerbreadths below the costal margin in the median line. It was hard, smooth, and painless. The spleen was markedly enlarged and the inferior pole was palpable. Like his sisters, he had none of the stigmata of congenital syphilis. The diagnosis made was familial hepatic cirrhosis. Professor N. Fiessinger, my learned colleague, confirmed my diagnosis and made several tests of the hepatic function. In April we saw the child twice. He was only subicteric but the urine was still somewhat deep in colour, pruritus was acute with lesions in the itching areas; the liver was very large measuring (by orthodiagraphy) with the child standing, 11·5 cm.; the spleen was large and dense measuring 9 cm. (child lying). The heart was normal in position but undersized for his age. In March 1938

the child was then aged 6 ; he measured 1·10 metres and was of ordinary proportions. The weight was unchanged—18·300 kg. Icterus was less marked than in the previous year, urine analysis showed permanent pigments and salts, the stools were pale or almost normal in colour. The hepatosplenomegaly persisted, extending three fingerbreadths below the costal margin, the liver (as measured by combined percussion and palpation) was 12 cm. in depth. The enlargement of the liver was chiefly of the left lobe and was the same as in the year before. The spleen extended 3 cm. below the ribs in the axillary line. On the screen its shadow was 8·5 cm. high instead of 9 cm. as in 1937. At this time there was no pruritus, the nails were marked by longitudinal ridges and furrows, corresponding to the dry and eczematous palms. The feet were not affected. Dental caries was noticed—as in his sisters. Further examination revealed irregular tonsils and dilated veins in the cheeks. For a year there had been no hæmorrhages and the boy was given 50 injections of anterior pituitary extract. Bleeding time three minutes. Capillary fragility test normal. Red blood-cell and leucocyte count normal. Fragility test normal (initial hæmolysis at 4·4 in April 1937, at 4·2 in March 1938).

Chemical examination of the blood :—

Blood-sugar (fasting)	1·03	Per 1,000 parts
Bilirubin (0·006 normal)	0·020	
Urea	0·31	
Total protein	52·31	
Serum albumin	33	
Globulin	19·3	
Albumin quotient	1·7	
Total lipoids	8·20	
Cholesterol	1·85	

Hepatic examination : The galactose test done by Professor Fiessinger on April 13, 1937, same dose as for adults.

Time	Urine	Concentrations	Galactose
8 to 10 a.m.	170 c.c.	6·7 per 1,000	1·14
10 to 12 a.m.	140 c.c.	14·9 per 1,000	2·09
12 to 6 p.m.	100 c.c.	2·2 per 1,000	0·22
6 to 8 p.m.	280 c.c.	0	0
	690 c.c.		3·45

Blood-sugar : After a dose of 10 grm. glucose the quantity rose from 0·52 grm to 1·10 grm in an hour and three-quarters. After a subcutaneous injection of adrenalin (½ mgm.) the blood-sugar rose from 0·62 to 0·90 per 1,000 (normal increase 0·40 grm. for 1 mgm. of adrenalin for adults).

Stools examination in January 1938 showed a trace of bilirubin and defective digestion of fat. In March 1938 the stools showed stercobilin.

Two cholecystographic examinations were made in March 1938 (fractional method) and were well tolerated. At the first attempt the gall-bladder showed no opacity. This was probably due to an insufficient dose of tenebryl. The second test (with 5 grm. of fluid) showed a normally opaque gall-bladder. In the skiagrams taken thirty, sixty, and ninety minutes after the opaque meal (Boyden) the shadow was noticeable, shrinking progressively. The bile-ducts were not visible.

To recapitulate : Among the six children, two, the eldest daughter Odette (aged 23 years) and the fifth child Ginette (aged 11 years) are perfectly healthy and normal. We cannot diagnose the cause of death in the case of the second child, Albert, who died at the age of 8 months, for we never saw him. We know that he grew slowly, was subicteric, and had a large liver. We may well presume that the child died of the same familial disease. Gisele and Fochette, the two girls who were under observation for five and nine years respectively until their deaths, and Jean the youngest child who, after being healthy for the first three years of life, now suffers from the same disease as his sisters, all present the same clinical picture. A large and hard liver, an enlarged spleen, intense icterus with colourless stools, retention of bile pigments and salts in the ducts

with excessive elimination of the same in the urine, intense pruritus and secondary eczematous lesions accompanied by scars from scratching. Also a tendency to hæmorrhages.

This clinical picture was presented by the two girls Gisele and Fochette. Both of them had intense icterus with colourless fæces, an enlargement of both liver and spleen, and consequent abdominal distension, pruritus, tendency to hæmorrhages (especially from the gums). The two girls were also greatly retarded both in mental and physical development and one of them was slightly deaf and had clubbed fingers.

The various biological tests made on these children threw no light on the pathogenesis of the disease. Cholesterinæmia was normal, lipæmia (tested in one case) increased. Protidæmia (tested in the same case) was lowered, although the albumin quotient was normal. Slight disturbances of the carbohydrate metabolism were also noticed in this child ; the fragility test was normal in the boy's case, increased in the two girls.

This family, in which we find hepatosplenomegaly, icterus with retention of bile pigments and salts, and in the more severe cases retardation in growth, weight and mental development, and some clubbing of the fingers, is a good example of " biliary cirrhosis of familial type."

But whereas the two eldest girls had a fatal disease with early onset (first months of life) and a serious retardation of development, the third patient, the boy, suffers from a mild form of the same disease which began only at the age of 3.

The history of this family, first published by Semelaigne, Lamy and myself in 1930 and completed by P. Seringe and myself last year, has prompted M. D. Olmer of Marseille to publish the following cases :—

A young man (aged 25 years) and his sister (aged 23 years) both gave a history of hypertrophic cirrhosis of the liver with icterus and splenomegaly, but with no tendency to hæmorrhages, no disturbance of development and with good general health.

Subsequently M. and Mme Chevrel and R. Aubin (Rennes) published the case of a child who not only suffered from biliary cirrhosis but was also a mongoloid imbecile.

In this family, among five brothers there was another 8 years old who, in addition to being a mongol, also exhibited an enlarged liver and spleen but had no other cirrhotic symptoms. Another child, aged 2, died jaundiced, with œdema, ascites, a large liver and spleen with an obvious abdominal collateral circulation. The autopsy revealed a small, firm, and smooth liver and a large spleen (the histology will be described later).

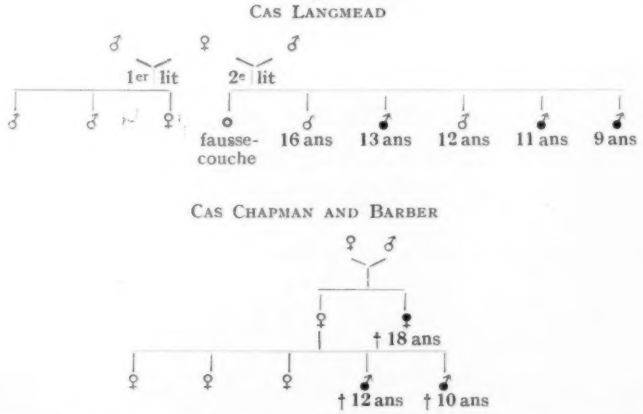

Fig. 1.—Genealogical tables of familial cirrhosis (latest French observations).

Such are the cases which have been recently published in France. They are complementary to our own. In reviewing the literature of the subject we have found 81 cases of children or young people derived from 32 families, who were subjects of hepatic cirrhosis, and no doubt this list is incomplete.

In 1902 P. Lereboullet pointed out in his book "Les cirrhoses biliaires" the familial tendency of cirrhosis. He admits the cases of Hasenlever, Parkes Weber, and Finlayson, but rejects the earlier cases of Howard and Jallye, not considering them as examples of this disease.

Several years later Osler and Bramwell suggested that these cases of familial cirrhosis might be explained as an abortive type of Wilson's disease, and this hypothesis has been supported by Lhermitte and Muncie, who thought that the cases which they studied afforded confirmatory evidence.

Most cases of familial cirrhosis have been published within the last ten years, and the largest contribution has been made by British and American authors, most of them members of this Society.

The disease affects boys twice as frequently as girls. In the families attacked the affected children are arranged in no definite order. In slightly more than half the families two children were affected, in other cases three and sometimes four. I have only noted one instance of twins being affected, and this is a doubtful case as the children began to take alcohol at a very early age.

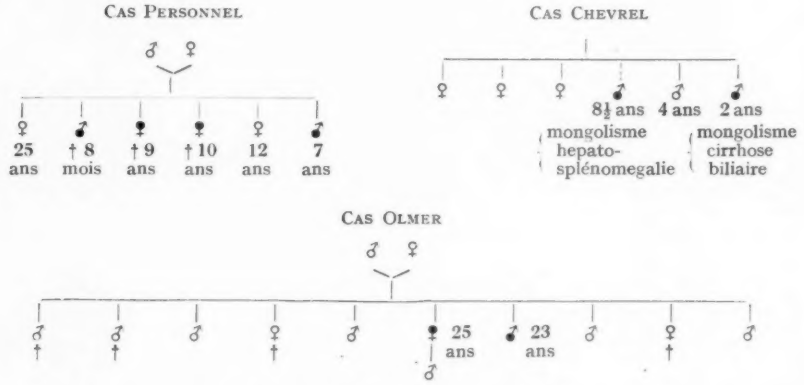

Fig. 2.—Genealogical tables of familial cirrhosis.

There are very few families in which two generations are affected. In one case a father and two of his children (Boinet); an aunt on the mother's side and her two nephews (Chapman and Barber); a mother and her son (v. Bogaert). These are, as far as I know, the only examples.

The first symptoms of the disease may appear either in infancy, childhood, or adolescence, but members of the same family are affected almost at the same period even although they belong to different generations (e.g. Chapman and Barber's case). This very curious fact makes us accept the influence of a congenital factor. Moreover, in the same family there is a striking similarity between the cases; symptoms and evolution are identical. But sometimes while there is one typical case there are others with milder clinical manifestations, such as a hepatomegaly which is only detected by the systematic examination of all the family. So it may be that a number of such cases have been missed.

From the geographical distribution of the published cases it may be said that familial cirrhosis occurs rarely in France and Germany, more frequently in England and America, and is unknown in Spain and Italy. But it is probable that it is commonest of all in India and Mexico.

Clinical forms.—If we neglect certain details we can establish three different types of familial cirrhosis.

(1) Cases in which the symptoms resemble Laennec's type of cirrhosis as found in adults, i.e. there is prominence of the abdomen, abdominal ascites, and more rarely dilatation of the venous system as shown by the presence of a caput medusæ. This syndrome suggests Laennec's but with a large liver (*Laennec's hepatomegalic cirrhosis*). Jaundice is frequently present. Van Bogaert's two series of familial cirrhosis are the only cases of familial cirrhosis with a small liver ; his patients were adults. Dickfeld's case can be included in this type ; so can Halbertsma's (three children in the same generation affected ; a girl aged 7 with a large and firm liver, and a girl aged 4½ with a large and firm liver, a large spleen and urobilinuria, and a third girl with a large liver, a large spleen, ascites, hæmatemesis, and epistaxis, who died of icterus gravis). Opitz's case can also be included here. A girl aged 8 and her brother aged 4 similarly affected—a prominent abdomen, large liver and spleen, ascites, anæmia, and slight jaundice with a tendency to hæmorrhages. Such cases are uncommon.

(2) Less rare are the familial cases presenting enlargement of the liver and spleen and hæmorrhages of the digestive tract, but without ascites or jaundice. Such cases can be labelled as *hypertrophic splenomegalic anascitic and anicteric cirrhosis.* F. Langmead published in 1934 an example of this type ; three boys out of a family of five with a large firm liver, finely nodular ; a very large spleen, but with no icterus, ascites, or anæmia. Other examples of this type have been given by Lee Smith, Szanto and Gunn. In such cases, which are comparatively slow in evolution and seldom rapidly fatal (an exception is Gunn's case in which death supervened within a year), splenectomy has been advised. Langmead has reported this operation being performed on two children and also on adults suffering from acquired cirrhosis with symptoms very similar to the familial disease. These cases recall Banti's syndrome. Here, however, the morbid process begins in the spleen, hepatic cirrhosis appearing only secondarily. Hæmorrhages of the digestive tract are frequent and call for operations on the spleen.

(3) To the third group belongs the family of which I have already given the clinical history. Other cases have been published by Hasenclever, Parkes Weber, Bramwell, Bamberger, Chapman and Barber, Bridgeman and Robertson, Lightwood and Loots, Paterson, Chand, Boinet, Olmer, Chevrel, &c.

In these, jaundice is a constant and prominent feature ; bile pigments and salts are abundantly present in the blood and urine, the saline impregnation of the skin being shown by the intense pruritus. The stools may be colourless, normal, or deep in colour. There may be stercobilin or traces of stercobilin accompanied by defective fat-digestion. The liver and spleen are definitely enlarged, firm and smooth. Ascites, œdema and hæmorrhages (especially the last mentioned) appear only in advanced stages.

These cirrhoses are rightly termed *biliary cirrhosis.* Many cases of familial cirrhosis have been called Hanot's syndrome. This syndrome has been shown by Gilbert, Fournier and Lereboullet to occur in children. In Hanot's disease febrile attacks, acute pains, arthropathies, and clubbing of the fingers are often noticed. These symptoms are not so common in familial cirrhosis, although febrile attacks are sometimes mentioned and we noticed clubbing of the fingers in one of our cases. Atrophy of the liver is equally uncommon both in familial cirrhosis and in Hanot's disease. But there are also intermediate types of familial cirrhosis and the clinical aspect may be typical in one member of a family and remain atypical in another. It is therefore difficult to accurately define the various types.

Disturbances of development.—To these essential clinical features of the disease we must now add disturbance of development.

(*a*) *Physical retardation :* The weight and height increase very slowly and often stop after the onset of the disease, as in the two girls under my observation. In Chand's case the eldest boy had retarded growth from the age of 7, i.e. four years before the onset of hepatosplenomegaly, jaundice, and pruritus. When he died at the age of 24 he was like a child of 13. The second boy at the age of 16 had the development of a child of 12 (the disease had begun two years previously). The third boy is 12 and looks like 8, he has been ill for four years. The boy and his two sisters who were reported by Hasenclever were also stunted.

(*b*) *Sexual development :* When the affected children reach puberty sexual development is retarded. In the family reported by Chand, the eldest boy (16) lacked his secondary sexual characteristics ; Szanto described genital hypoplasia in a boy aged 15.

(*c*) *Mental development :* The impairment of mind and movement is sometimes evident in infancy. Our own young patients were backward both in walking and talking. One did not walk till over 3 years old, the other not till $2\frac{1}{2}$, and talked later still. We have thus established a syndrome, although not constant, of " hepatic dwarfism " or of " dwarfism with infantilism and mental retardation ". To trace the relationship between the abdominal changes and the stunting of physical, sexual, and mental development we must study the evolution of cirrhosis.

Evolution.—Disturbance of physical development may be the first manifestation of biliary cirrhosis. Usually digestive disturbances mark the onset. Anorexia is the commonest symptom, diarrhœa is not so frequent ; vomiting and abdominal pains are rare. The hæmorrhagic diathesis—when present—appears early, being sometimes the first sign of disease. This takes the form of epistaxis, hæmatemesis or melæna, or a combination of all three (e.g. three cases of Chapman ; one of Chand, and one of mine). The parent's suspicion is sometimes aroused by the abdominal distension. Sometimes hepatosplenomegaly is evident and there is no history of the visceral condition at birth or in the period preceding the onset of symptoms. The clinical picture may remain unaltered, or more often icterus appears, and in several cases the pre-icteric period has passed unnoticed, jaundice being the first symptom to attract attention.

In most cases hepatosplenomegaly remains constant and conspicuous and only in a few cases do authors mention a shrinkage shortly before death. The patient usually dies in a condition of extreme cachexia, sometimes with hæmorrhages or ascites, either with or without œdema (e.g. Finlayson's and Chand's cases).

This is the usual course of biliary cirrhosis. The other familial cirrhosis, anicteric and anascitic cirrhosis and ascitic cirrhosis evolve in almost the same way. The fact that some authors consider the fatality rate of these cirrhoses to be lower may be due to the small number of cases recorded. In about half the cases of familial biliary cirrhosis death occurs within a few years of onset (maximum ten years, minimum one year). Recovery has never been reported. The course can be rapid or slow. The onset can appear early or later in life, and here we must mention the possibility that cirrhosis of the liver in the adult may be of hereditary origin.

Pathology.—Histological observations of familial and hereditary cirrhosis are few in number.

In Chevrel's case, the liver on section appeared greatly damaged. The lobular arrangement was destroyed. The cellular supporting trabeculæ had vanished. The cells were much smaller in number and had lost their coloration affinity. The cytoplasm still took acid dyes, whereas the nuclei hardly took basic dyes. The cells varied greatly in size : some were very large, others did not exceed the size of a pea. Their shapes were also various. The cytoplasm was friable, and frequently dotted with biliary pigment. Bile is also to be found in the small biliary ducts. The

remaining cells were either packed closely together or, and this is a more frequent arrangement, separated, dissociated one from the other by newly built tissue. This tissue, very abundant, rather tough, full of collagen fibrils had, in some places, the aspect of a ring around small foci of hepatic cells. The nuclei were scanty and did not take the dye. Some venous lumena were obstructed by a loose network of endovascularities. The epithelia of the biliary vessels were the only elements whose nuclei had kept the coloration affinity. No inflammatory process was found.

In Calvin and Saffro's case (boy of 11 suffering from hepatic cirrhosis of non-familial type), biopsy revealed lesions confined to the portal and periportal areas, inflammatory reactions of the bile-ducts and of the surrounding tissues.

Diagnosis.—In diagnosing accurately hepatic familial cirrhosis, the clinician must bear in mind several distinct alternatives. He must exclude the group of *dyslipoidic diseases* such as Nieman-Pick's disease, Gaucher's disease, Tay-Sach's, and others. Among these metabolic disorders of congenital origin we will only mention here Gaucher's disease. The family incidence of this disease has been reported. Clinically it is distinguished by splenomegaly, sometimes by hepatomegaly, pigmentation of the skin, and hæmorrhages. The difference lies in the fact that the splenomegaly is more marked than the hepatomegaly, the tendency to hæmorrhages is more conspicuous, adenopathy and changes in the bones are frequently reported and there is no icterus, but there is hæmochromatosis.

Familial cirrhosis may also be mistaken for *hæmolytic disease*. Here again we find a familial incidence, hepatosplenomegaly, icterus, attacks of anæmia, and of fever. However, examination of the blood revealing modification of the cells, with reduced resistance to salt solution, the relatively small liver in proportion to the enormous spleen, and the clinical course will prevent any such error.

We have named the condition " polycoric " from the Greek *πόλυ many* and *κόρος satiety*, the pathological accumulation of reserve substance ending in hypertrophy. The most typical example of polycoric hepatomegaly is v. Gierke's glycogenesis (which was noticed by Snapper and v. Crefeld before the German pathologist) and massive hepatic steatosis (as described by Semelaigne and myself). This polycoric hepatomegaly can be a familial disease and give rise to an enormous abdomen and to disturbances in growth. But in such cases there is no splenomegaly, a symptom always observed in a child with cirrhosis of the liver (Smith and O'Flynn, Poynton and Willie). I must also mention a syndrome which Marcel Lelong has named " de Toni-Debré-Fanconi's syndrome " in which there are disturbances in glycæmia and also a hepatomegaly. We have at present such a case under observation. It is differentiated from infantile anicteric anascitic cirrhosis principally by the absence of splenomegaly and in the later stages by the marked changes in the bones and disturbance of metabolism and renal function. Cirrhosis must not be mistaken for the hepatomegalic syndrome with mental disturbances, changes in the bones and corneal opacities which has been described before this Society by Poynton, Ellis, Lightwood, Sheldon and our President, E. A. Cockayne. In this we find hepato-splenomegaly togetherwith corneal opacities, changes in the bones (large head with prominent frontal bones), insufficient depth of the glenoid cavities of the scapula and ilium, and also stunted mental development. But there is no icterus and no sign of obstructed portal circulation. This condition is not that of cirrhosis of the liver, but reminds one of a fatty infiltration of the liver, and up to the present this new syndrome, whose morbid entity is not yet defined, has not presented a familial incidence.

Before closing the chapter on diagnosis we must distinguish familial cirrhosis from the other cirrhoses of childhood. In some cases the diagnosis is easy enough. Hutinel's cardio-tuberculous cirrhosis, fatal to tuberculous children, for example, starts with pleurisy. Cirrhosis in a newly born infant with inherited syphilis and exhibiting cutaneous lesions, alterations in the kidneys, and a characteristic

appearance, is also easily distinguished. But when cirrhosis is detected in a child, even if a familial case, we should first consider infection, e.g. hereditary syphilis, or an intoxication such as alcoholism. Hereditary syphilis might possibly cause cirrhosis in an infant or child. Our French tradition, up to recent years, permitted this explanation. But these cases are quite exceptional. As regards alcoholism, the possibility may be admitted. Rolleston and Ely have demonstrated it in children who have been given alcohol regularly and liberally by their parents.

Among the cirrhoses of infective origin there is one very curious type; this is cirrhosis following catarrhal epidemic icterus. A. Wallgren has recently described several examples of this disease. The child is attacked along with other children by an infective catarrhal icterus. The attack seems moderate. The child recovers to lead a normal life. Then appear fits of acute jaundice, with epigastric pains and enlargement of the spleen, and the child dies from gastro-intestinal hæmorrhages. Post-mortem examination reveals a nodular cirrhosis. The course of the illness and the atrophy of the liver enable us to diagnose these exceptional cases.

In order to throw some light on the pathogenesis of hereditary and familial cirrhosis of the liver, we will consider the following conditions, which have been already admirably dealt with by Parkes Weber :—

(*a*) Obstructive cirrhosis due to a congenital defect of the extrahepatic bile-ducts.
(*b*) Cirrhosis of the liver in young Indians.
(*c*) The syndrome of hepatic lenticular degeneration.
(*d*) The syndrome of cirrhosis of the liver combined with hæmangiomatoses.
(*e*) Renal sclerosis with dwarfism.

(*a*) Obstructive cirrhosis of the liver due to a congenital defect of the extrahepatic bile-ducts. In the case of the three children under my own care the stools were usually colourless. So we wondered whether these might not be cases of obstructive cirrhosis due to a congenital deformity of the bile-channels. Infants suffering from congenital deformity of the bile-ducts combined with a definite cirrhosis of the liver have been recorded (Legg, Thomson, Howard and Wohlbach). Hatfield records two brothers, who died when 13 days old, and McKay a brother and two sisters, who both died within a month of birth all from this condition. Children suffering from icterus due to a defect in the bile-ducts cannot live long; fourteen months at the utmost (MacMahon). This author, who has had ten such cases, says that jaundice may be deferred in onset as much as a month after birth, even with asthenia, although the secretion of bile usually starts in the third month of intra-uterine life. Possibly a more minute examination might reveal some definite anomaly to explain these facts. The investigations of Lightwood and Loot favour this theory. In an infant aged 22 months who died with hepatosplenomegaly, and who had been stationary in weight for a year, but who had no ascites, they found post mortem, in addition to numerous small cysts of the renal cortex, a diffuse fibrosis of the liver and enlarged bile-ducts, giving to the cut surface a cystic appearance. The brother and sister of this patient suffered from hepatosplenomegaly.

In congenital cirrhosis of the liver, if the icterus suggests an obstructive jaundice, one must bear in mind the possibility of an added anomaly of the bile-channels. The obstruction of the bile-channels may not be always responsible for such a type of cirrhosis; there may be a deformity of the bile-channels combined with congenital cirrhosis.

(*b*) Cirrhosis in young Indians is a difficult problem. During the last forty years our English and Indian colleagues have published some interesting observations on cirrhosis of the liver in childhood as found in India (Gibbons, Manson, Mackenzie, Glose, Pearse, Tyer, Pandalai, Tirumurti and Radhakrishna Rao, Chand, Forsyth, Rezek, &c.). Such cases also occur in Mexico. There are three stages in the evolution of this cirrhosis: the first is indefinite, with loss of appetite,

fever, slow and painless enlargement of the liver. The second is marked by attacks of fever, subicterus, and progressive enlargement of the liver and spleen. In the last stage there is obstructed portal circulation, icterus gravis combined usually with absence of colour in the fæces. The prognosis is unfavourable ; death is almost uniformly the end and is ushered in by coma rather than by hæmorrhage. The discussions on the ætiology of this disease have been endless. Its family incidence has often been reported (Manson). The influence of food and spices has been disproved, but it may well be that there is in India just the same hereditary disease, but with a higher frequency.

(*c*) Hepatic lenticular degeneration. The relationship between familial cirrhosis of the liver and hepatic lenticular degeneration is of great interest ; we now realize that under this head we should include such diseases as (1) Wilson's disease with its usual clinical features—involuntary movements, contractures and tremors, muscular rigidity, generalized asthenia, and concealed cirrhosis. (2) Westphal-Strumpell's pseudosclerosis, characterized by the peculiar shaking, poor motor response when at rest, spasm of associated antagonistic muscles, contractions, and convulsive fits. (3) Certain other syndromes such as the progressive torsion spasm (Walgren), mental disorders associated with extrapyramidal rigidity (Lhermitte and Muncie).

One feature common to these three types is the ocular lesion, i.e. the Kayser-Fleischer bronzed corneal ring. This is inconstant but frequently reported and characteristic of the disease ; it is sometimes only revealed by autopsy. The familial incidence of the disease has been reported in numerous cases.

L. van Bogaert studied the heredity of the disease and found it to be a recessive trait, often heteronymous. He reports that the evidence for the familial character of the disease is overwhelming, and that the morbid trait is transmitted to all males without exception, while the females are totally exempt. Sometimes nearly all the children in a numerous family are affected (Lhermitte and Muncie, F. J. Curran).

The symptomatology of Wilson's disease with its concealed cirrhosis and its unconcealed renal disorders, is not well defined. Some cases have an abdominal, others a hepatic or portal form. This signifies that the hepatic manifestations of cirrhosis have been clearly observed by the clinician while the mental disorders have been mild or doubtful and may only have become obvious towards death. Lhermitte shows that while the symptomatic combination of hepatic lenticular degeneration involves three major factors, i.e. liver, brain, and cornea, it is natural to expect quite a number of clinical types according to which two of the three factors are present. This leads us to admit the existence of a type of familial cirrhosis with splenomegaly but without corneal or cerebral changes, and may also imply a relationship between our infantile familial cirrhosis and the nervous hepatic and corneal syndrome of Wilson and Strumpell and Westphal's group. A case reported by Lhermitte and Muncie is especially convincing : The brother of a patient suffering from typical Wilson's disease showed at the age of 38 the symptoms of a splenomegalic ascitic cirrhosis, with slight arcus senilis ; their sister had died at the age of 22 from hepatic cirrhosis with ascites, often relieved by paracentesis. We should bear in mind the importance of accurate neurological and ophthalmological examination in all cases of familial cirrhosis, and in all cases of infantile cirrhosis and their families. Careful microscopical examination of the affected organs is also important.

(*d*) There is another morbid entity which may be related to the disease now under discussion. L. van Bogaert has with J. Scherer recorded a family suffering from hæmorrhagic hæmangioma or Rendu-Osler's disease. Both mother and son had splenomegaly. A post-mortem examination of the son showed a Laennec's cirrhosis, whereas the mother still alive, showed a pure cirrhosis. In these cases we have to exclude the possibility of both patients being attacked by the same toxic agent. L. van Bogaert remarks that post-mortem examinations of Rendu-Osler's disease are rare. Still in three cases severe lesions of the liver have been noted—twice

acute yellow atrophy, once a carcinoma. Telangiectasis and vascular dilatation frequently appear in the course of and even at the onset of cirrhosis. These telangiectases may be the result of mechanical changes in the venous circulation. There may be a biological link between these two types of disturbance, cirrhosis of the liver on the one side and the condition of the venous and capillary system on the other. L. van Bogaert goes so far as to postulate a biological interdependence between cirrhosis of the liver and hæmangiomatosis. Parkes Weber examined this problem very thoroughly and he brings his personal experience to confirm L. van Bogaert and Scherer's theory. Our cases of familial cirrhosis of the liver in childhood and youth resemble sometimes Laennec's cirrhosis, sometimes Hanot's cirrhosis, or splenomegalic cirrhosis. In the strange " muddle " (P. E. Weill) known as Banti's syndrome the types are more or less confused. In a number of these cases especially, perhaps in Hanot's cirrhosis but also in hæmochromatosis and bronzed diabetes, the ætiology is a mystery to us. There is no trace of infection or intoxication. Is there a constitutional, or rather a hereditary factor as Parkes Weber suggests ?

(*e*) When we look for the same pathogenesis in other organs such as atrophic cirrhosis of the kidney in a child (chronic nephritis with renal dwarfism), the problem of the pathological physiology is the same as in biliary cirrhosis substituting the kidneys for the liver. The resemblance between these two forms of hereditary cirrhosis is extremely striking as in both diseases we find, combined with a progressive visceral sclerosis, defects of the excretory channels, neuroglandular disturbances such as dwarfism and infantilism, and even mental subnormality. We may therefore think that just as in cases of renal sclerosis of congenital origin, some defect of the trophic centres may also be the cause of visceral sclerosis in the liver. Some trophic change is responsible for polycoria, dyslipoidæmia, atrophy or hypertrophy of extremities and organs. In hereditary sclerosis of the kidney, as in congenital sclerosis of the liver, the disease is progressive. Sooner or later the clinician notes its apparently spontaneous appearance. It becomes gradually more and more severe and generally ends in death because it is seated in an organ of vital importance. In such cases the impairment of function affects the metabolism and causes a storage of reserve substances (fat or glycogen), degeneration of the parenchyma in some places, sclerosis in others, atrophy in one organ, hypertrophy of another. I believe that a hereditary progressive malformation is the central neuro-hormonal cause of numerous diseases including hepatic cirrhosis, the origin of which we have sought in vain in possible infections. The pathology of the phenotype so familiar to us must be linked with that of the genotype. A closer study of genetics may help us in many such problems.

Section of History of Medicine and Clinical Section

JOINT MEETING HELD ON MARCH 1, 1939

Chairman—DUNCAN FITZWILLIAMS, C.M.G., F.R.C.S. (President of the Clinical Section)

The History of Clinical Medicine (Principally of Clinical Teaching) in the British Isles

By Sir HUMPHRY ROLLESTON, Bt., G.C.V.O., K.C.B., M.D.

THE history of Clinical Medicine (principally of clinical teaching) in the British Isles, is a very wide subject. "Medicine" here must mean the whole field of physic, surgery, with their specialist branches, and therefore cannot be attempted in detail by an opening paper. The discussion has two main but closely allied subjects: the history of clinical medicine and the history of clinical teaching. Clinical medicine is the oldest form of medicine from which morbid anatomy and pathology and its modern subdivision, preventive, curative, and symptomatic treatment, and the recent clinical science have been derived. It goes back to Hippocrates as we are reminded by the adjective "Hippocratic" in phrases, such as Hippocratic face and fingers, and the physical sign of succussion. Greek medicine spread in various directions, especially to Alexandria in the time of Herophilus and Erasistratus (fourth century B.C.) and thence to Rome during the lives of Asclepiades (124–40 B.C.) and Galen (A.D. 130–201); where though there was no compulsory regulation about clinical attendances, the existence during that period of some bedside instruction is supported, for what it is worth, by the often-quoted epigram (Ep. v. 9) of Martial (A.D. ?40–103), thus translated by Raymond Crawfurd

> I lay ill; but soon Symmarchus sought me
> With a class of a hundred young men,
> Whose hundred cold paws have brought me
> The fever I lacked till then.

The lamp of Greek medicine reached Spain from Arabia (700–1200) and the school of Salerno (1000–1200) of obscure origin became a notable centre.

The Influence of Padua.

Then came the period of activity of the Italian Universities in medieval medicine, first at Bologna in the middle of the twelfth century and especially at Padua in the sixteenth century, where at the hospital of St. Francis about 1543 the humanist Joannes Baptista Montanus or della Monte (1498–1552) began to teach clinical medicine at the bedside. This tradition, after a temporary lapse, probably due to Montanus' death, was followed by Marco degli Oddi (1526–1591) and Albertino Bottoni (d. 1596).

Influence of Leyden.

Jan van Heurne (1543–1601) of Utrecht went to Padua in 1567, was a pupil of Fabricius ab Aquapendente (1537–1619), the anatomist and Oddi, and in 1571 received the doctorate of medicine. He then remained in Padua as body physician to a rich nobleman for two years, and was about to become a professor in the University, but the jealousy of his rivals made him adopt the better part of valour and leave Padua secretly for Utrecht, where he practised medicine until in 1581 he was called to the chair of medicine and anatomy at Leyden. There he was the first to give demonstrations in human anatomy, and also initiated bedside clinical instruction, though the facilities in this respect were but scanty. Even in Boerhaave's time there were twelve beds only available, contained in two wards, one for men and the other for women, in what is now the St. Caecilia Gasthuis (Sigerist). Heurne was an ardent follower of Hippocrates, and among his publications were six on the aphorisms and other works of the father of medicine. As a clinical teacher he was followed by his son Otto (1577–1652) who succeeded him as professor, by Franciscus Sylvius (1614–1672) who established the first chemical laboratory in Europe and may be regarded as a founder of the iatrochemical school, by G. Bidloo (1649–1713), professor of anatomy and surgery, and by Hermann Boerhaave (1668–1738), the Dutch Hippocrates, who was appointed professor of the institutes of medicine (physiology) in 1701, and professor of medicine in 1709. Gerhard van Swieten (1700–1772), a native of Leyden and a devoted pupil of Boerhaave, carried the teaching of clinical medicine to Vienna, and established hospital instruction. Later, mainly by the initiative of Corvisart, Auenbrugger's account of percussion became known in Paris. Boerhaave's Edinburgh disciples on their return home introduced into the " modern Athens " both the teaching of physiology, the chair, founded in 1726, taking its name from Boerhaave's book of 250 pages *Institutiones Medicae* (1708), as pointed out by Fulton, and also, as will be described later (p. 47, last para.) the bedside instruction in clinical medicine.

How Clinical Medicine and Bedside Teaching Came to England.

Clinical medicine may have been imported into this country from Padua and Leyden, and also later from Vienna and Paris by British students who, as was often the case in the sixteenth, seventeenth, and eighteenth centuries, studied medicine on the Continent. There were, however, outstanding early examples in this country of individual and independent clinical genius.

Thomas Sydenham (1624–1689), whose clinical genius has been recognized by epithets, such as the British Hippocrates and the Reformer of English Medicine (G. Newman, 1924) was a sturdy independent puritan, who may have begun his devotion to " the divine old man " (Hippocrates) when in contact with Robert Boyle (1627–1691), John Locke (1632–1704), and others at Oxford, and been confirmed in this conviction by a visit in about 1659 to Montpellier, where under the popular protestant professor Charles Barbeyrac (1629–1699) Hippocrates was, contrary to the tendency at other French schools, followed in preference to Galen.

William Heberden the elder (1710–1801), called by Osler the British Celsus, was the first to give an account of angina pectoris (1768) and was the author of the *Commentarii de morborum historia et curatione*, completed in August 1782 but not published until 1802 when his son William the younger (1767–1845) saw them through the Press and translated them into English. The way in which the commentaries were written is instructive ; they were built up gradually from notes taken in Latin during his active professional life in the chambers of the sick, from themselves or from their attendants. These were read over every month and expanded or modified as subsequent events made necessary. " It appeared more advisable to give such facts only, as were justified by the original papers, however imperfect, than either to supply their defects from memory, except in a very few instances, or than to

borrow anything from other writers." This is a high ideal; and he was aptly described as "that grave figure with the mind of a philosopher and the heart of a child" (Hingston Fox).

Bedside teaching at Padua may have reached Great Britain through more than one channel. John Caius (1510–1573) went to Padua in 1539, lived for eight months in the same house as Vesalius (1514–1564), who was then preparing the *De fabrica humani corporis* (1543), and thus became inspired as an anatomist. He followed the practice of Montanus, whom he spoke of as his principal teacher, and while in Padua wrote *De medendi methodo libri duo, ex CL. Galeni Pergameni et Io. Baptistae Montani Veronensis principum medicorum sententia* (1544) which dealt with the general system of the practice of physic based on the principles of Galen and Montanus. Although Caius was physician to three sovereigns—Edward VI, Mary and Elizabeth—President of the Royal College of Physicians of London for nine years, and a busy practising physician, he did not teach medicine at the bedside; indeed until the second half of the sixteenth century or early in the seventeenth century the staffs of the two large hospitals in London were composed of surgeons, and the first appointment of a physician at St. Bartholomew's was in 1567 and at St. Thomas's in 1620. At St. Bartholomew's Roderigo Lopez, a Portuguese Jew, physician to Queen Elizabeth, was hanged, drawn, and quartered in 1594, for designing to poison her, and has been regarded as the probable original of "Shylock" in the "Merchant of Venice". This depressing start should have been corrected in 1609 by the appointment of William Harvey. Caius, though he lived in the parish of St. Bartholomew the Less, was never officially connected with the hospital on that site. Until the eighteenth century there were few hospitals available for clinical medicine or bedside teaching. Caius may perhaps be regarded as having prepared the way in an indirect and remote manner for the eventual development of clinical medicine; he brought Vesalian anatomy to London and taught it for about twenty years from 1545 at the Barber-Surgeons Hall. The monopoly possessed by the Barber-Surgeons of teaching anatomy and surgery, lapsed with the separation of the surgeons from the barbers in 1745. Then private schools for the teaching of anatomy, to which surgery and eventually medicine were added so as to constitute "complete" schools, sprang up, especially the Hunterian Great Windmill Street school and the Graingers' Webb Street school. In many instances the proprietors were on the staffs of London hospitals, and they naturally obtained the help of their hospital colleagues, and in the nineteenth century these private schools became the medical schools of the hospitals, for example the London, Middlesex, and St. George's. In some instances, especially at first, the instruction was mainly by lectures; for there may have been some reluctance on the part of the Governors to allow bedside instruction inside the hospitals of London. At any rate at the London Hospital, founded in 1740 by John Harrison (1718–1753), Sir William Blizard (1743–1835), who had been elected surgeon to the hospital in 1780, obtained permission from the House Committee to deliver lectures on anatomy and surgery in "the demonstrating theatre" of the hospital, but with the proviso that he should not make use of the patients in the hospital. Towards the end of the eighteenth century some physicians lectured in the hospitals to which they were attached, for example William Saunders (1743–1817) at Guy's, James Maddocks (d. 1786) at the London Hospital, and William Keir (d. 1783) at St. Thomas's, were lecturing in 1783 (Chaplin).

Influence of Edinburgh.

The main and immediate stimulus to the introduction of bedside teaching into Great Britain came from Leyden. In about 1718 among Boerhaave's many pupils was John Rutherford (1695–1779), maternal grandfather of Sir Walter Scott, and professor of physic at Edinburgh (1726–1765). In 1746, after the disturbances of 1745 had quieted down, he was the first to give clinical lectures in the Royal Infirmary,

formal permission being recorded in 1748. In 1747 Robert Whytt (1714–1766) was appointed professor of the Institutes of Medicine and also professor of Medicine, probably to help Rutherford, who retained the chair until 1765, but ceased to lecture formally in Latin when he began clinical bedside teaching (Comrie). Thus bedside teaching, which came to Leyden from Padua in company with anatomy, reached Edinburgh about 130 years later, together with physiology. In 1756 definite courses of clinical instruction were given in the Royal Infirmary by Rutherford, Whytt, William Cullen (1710–1790), and Alexander Monro primus (1697–1767).

Edinburgh thus became the medical Mecca of the British Isles in the second half of the eighteenth and first half of the nineteenth centuries, and among the students attracted there were future active spirits at two medical centres which they helped to make famous for teaching and research in clinical medicine. These were Richard Bright (1789–1858), Thomas Addison (1793–1860), and Thomas Hodgkin (1798–1866), the great triumvirate of Guy's hospital, and Abraham Colles (1773–1843), R. G. Graves (1796–1853), Sir Dominic Corrigan (1802–1880), and William Stokes (1804–1878) of Dublin. Graves and Stokes at the Meath Hospital were prominent in the initiation of bedside teaching and allowing students free access to the patients allotted to them for the reports for which they were responsible.

The Apprentice System and Bedside Teaching.

A hundred and more years ago students were admitted to the wards of the hospitals in London. There were different grades of these hospital students : (i) the surgeons' apprentices (for the physicians did not have them) had special privileges, such as a recognized claim for vacancies on the permanent staff, in return for the premium, £300 to £1,000, they paid ; (ii) surgeons' dressers who paid very much less (about ten guineas a century ago, Paget), and (iii) other students who " walked the hospital ", but without any claim on particular members of the staff. Sir James Paget (1814–1899) who entered St. Bartholomew's Hospital in 1834 as an ordinary student, wrote : " There was very little active practical teaching in the wards or by clinical lectures (in medicine) ; it was customary to think it sufficient to give opportunities for learning to those who could learn by looking on ". Peter Mere Latham (1789–1875), physician to the hospital, he described as coming down to the hospital at 8 a.m. three times a week and giving real bedside teaching, but added that otherwise there was very little else of what could be called clinical teaching of medicine.

Before the apprenticeship in general practice was abolished by the Medical Act 1858 there must have been considerable opportunities of bedside instruction given by the practitioners to their apprentices. No doubt the amount of instruction thus provided would have varied in accordance with the character of the individual practitioner.

The Paris Medical School.

In the last century, particularly in its first half, the Paris Medical School was a centre of great activity, and after the peace of 1815 attracted many British and other students and thus exerted a wide influence on clinical medicine and teaching. This was due to the reputation of P. C. A. Louis (1757–1872), P. A. Piorry (1794–1879), and of G. Andral (1797–1876) who organized clinical medicine as it is now known, and in his great *Clinique médicale* (1829–33) was the first to use the word *clinique* in its modern sense. Louis was noteworthy as the inventor of the numerical method which dealt with medical as distinct from vital statistics. At that time clinical observation as cultivated at Guy's, Dublin, and Paris was of a high order, and probably, being without the help now available from microscopes, laboratory tests, X-rays, and instruments of precision, except the new stethoscope, was all the more fully developed. Perhaps it is now almost forgotten that the present short clinical thermometer, which made it a routine to take the temperature, was invented in 1866 by Clifford Allbutt.

Oxford and Cambridge.

At Oxford and Cambridge, from their birth until the nineteenth century, medical teaching, such as it was, consisted in the reading and expounding of Hippocrates, Galen, and Aretaeus. Except at Oxford during the middle of the seventeenth century when the Philosophicall Clubbe (1651) and the activity of its members—mainly visitors driven there by the disturbed times—Robert Boyle, Richard Lower, Thomas Willis—there was not any scientific activity. The eighteenth century was particularly unsatisfactory from a medical point of view.

In the first half of the nineteenth century there were signs of awakening activity at the Universities. At Oxford John Kidd (1775–1851), Regius professor (1822–51) lectured on anatomy and not on medicine, was most anxious to further scientific and medical teaching, but could not make any way against the predominating classical stream. At Cambridge John Haviland (1785–1851), Regius professor (1817–51), was extremely active giving fifty lectures on pathology and the practice of medicine during the year.

Clinical Medicine and Percussion and Auscultation.

Physical methods of examination, though not neglected by Hippocrates as shown by his description of succussion, made little progress until morbid anatomy showed what were the changes in the body as was done by Théophile Bonet (1620–89) in his *Sepulcretum sive anatomia practica, ex cadaveribus morbo denatis* (1679), G. B. Morgagni (1682–1771) in his *De sedibus et causis morborum per anatomen indagatis* (1761), and Matthew Baillie (1761–1823) in his *Morbid Anatomy of some of the most important parts of the body* (1793). It may give some indication how slowly, as judged by modern standards, physical examination became a routine practice in this country to quote from the obituary oration given by Sir Henry Halford (1766–1844), president of the Royal College of Physicians, on December 22, 1823: "He (Baillie) appeared to lay a great stress upon the information which he might derive from the external examination of his patient, and to be much influenced in the formation of his opinion of the nature of the complaint by this practice. He had originally adopted this habit from the peculiar turn of his early studies; and assuredly such a method, not indiscriminately but judiciously employed, as he employed it, is a valuable auxiliary to the other ordinary means used by a physician of obtaining the knowledge of a disease submitted to him. But it is equally true that, notwithstanding its air of mechanical precision, such examination is not to be depended upon beyond a certain point. Great disordered action may prevail in a part without having yet produced such disorganization as may be sensibly felt."

A great event in the history of physical signs was that of percussion of the chest by Joseph Leopold von Auenbrugger (1722–1809) of Vienna, who published in a pamphlet of 22 pages his *Inventum novum ex percussione thoracis humani, ut signo abstrusos interni pectoris morbos detegendi* in 1761, the year in which Morgagni's great book *De sedibus et causis* appeared, and so it might now be imagined, should have been a means of correlating clinical manifestations with gross morbid anatomy; but though it was praised by von Haller and translated into French by Rozière de la Chassagne in 1770, it was long before its time. In 1808, the year before Auenbrugger's death, J. N. Corvisart (1755–1821) translated the *Inventum novum* again into French, which was reviewed by his pupil R. T. H. Laennec (1781–1826), who in 1819 brought out his equally epoch-making *L'auscultation médiate.* The method was introduced into Great Britain by Sir John Forbes (1787–1861) by his translation in 1821, who three years later performed the same paternal office for Auenbrugger's *Inventum novum*, then hardly known in England. In 1822 Hodgkin, who had learned auscultation from Laennec at the Necker Hospital, introduced it for trial at Guy's Hospital. William Stokes (1804–78) published his *Introduction to*

the Use of the Stethoscope in 1825, the year that he graduated at Edinburgh, and dedicated it to William Cullen. C. J. B. Williams (1805–89), another pupil of Laennec, dedicated his *Rational exposition of the physical signs of the diseases of the lungs and pleura* to Sir Henry Halford who, however, was never converted to its use. Auscultation did not make the headway it deserved, and as in the reception of Harvey's discovery of the circulation, and Lister's antiseptic method, it was only welcomed by young men. John Elliotson (1791–1868) devoted his Lumleian lectures at the Royal College of Physicians in 1829 to " The recent improvements in the art of distinguishing the various diseases of the heart ".

Another keen champion of auscultation was James Hope (1801–41), an Edinburgh M.D. who, after a year in Paris, where he learnt the art of auscultation, settled in London and became the first clinical clerk at St. George's Hospital in 1828, and was elected in 1834 to the new post of assistant physician to St. George's Hospital. With wonderful energy he taught, practised, and brought out an atlas of morbid anatomy (1834) and a *Treatise on diseases of the heart and great vessels* (1832) which went into a third edition the year after his premature death from pulmonary tuberculosis. He described a soft early diastolic murmur due to mitral stenosis and was the first to distinguish it from the diastolic murmur of aortic reflux. It was once called Hope's murmur. It is curious that though logically convinced that there should be a presystolic murmur in mitral stenosis, he was never able to assure himself of its existence.

The following items show that auscultation made its way slowly. Sir Thomas Watson (1792–1882) in his *Lectures on the Principles and Practice of Physic* (1843) said that except in certain circumstances, such as a dirty or infectious patient, " the use of the stethoscope for auscultation is rather a hindrance than a help "; this statement appeared in the fifth and last edition in 1871. James Arthur Wilson (1795–1882), physician to St. George's Hospital (1829–57) who from his initials J. A. W. signed anonymous articles " Maxilla ", is recorded by his son-in-law W. H. Dickinson (1832–1913) to have remarked after listening to a case of bronchopneumonia, " strange sounds, strange sounds ".

Many years ago when Sir Cooper Perry (1856–1938) and Lauriston Shaw (1859–1923) were analysing the old post-mortem records dating from 1826 at Guy's hospital, they came across records of cases of lobar pneumonia in which the demonstrator of morbid anatomy, obviously with reverent admiration for clinical insight, noted: " Dr. —— always said that the lungs were affected ".

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